Underexploited (ipso, ortho) Microbial Arene Dihydroxylation Uses in Synthesis & Catalysis

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Award date:
2013

Awarding institution:
University of Bath

Underexploited (*ipso, ortho*) Microbial Arene Dihydroxylation: Uses in Synthesis & Catalysis

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A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

2013

Signed …….. Date ……..

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Acknowledgements

This may be read first but it has been savoured and written last.

Much thanks and appreciation is deserved for my supervisor Dr Simon Lewis, for the continual help, support and scientific ideas.

Funding through the DTC (EPSRC) has allowed me to participate in all the 'otherthings' I have been lucky enough to be part of, enjoy and learn from. Namley the internship to Ethiopia, attendance at several international scientific conferences and all of the public enagagement and outreach activities. Working with other students, now at the end with good friends.

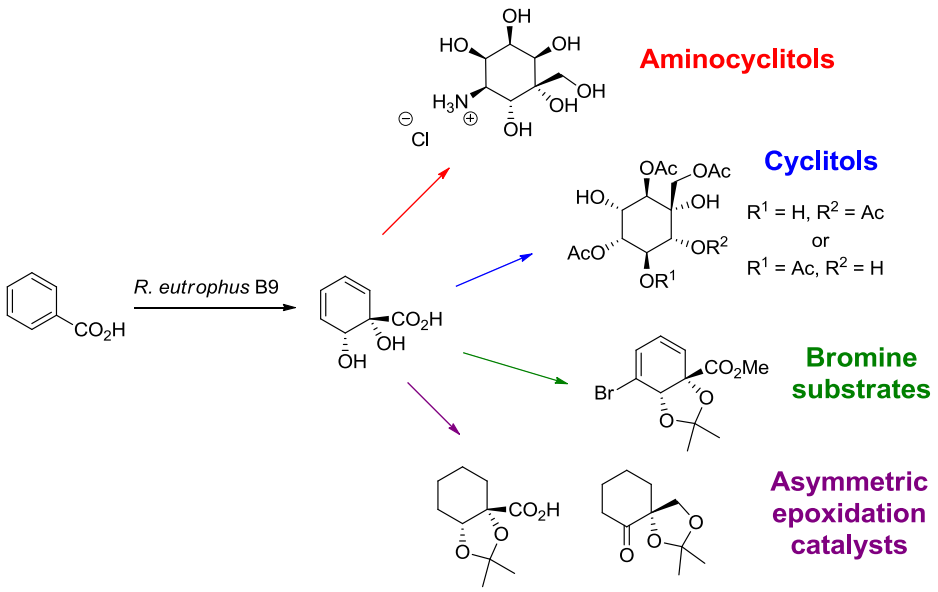
Thanks are also deserved for the individuals, family, friends and colleugues who have had significant input and influence both professionally and personally, they know who they are.

Abstract

This thesis sought to expand upon the synthetic application of the underexploited *ipso, ortho* diene *cis*-diol microbial arene oxidation product from benzoic acid.

The microbial oxidation of benzoic acid by mutant strains of bacteria to give the *ipso, otho* diene cis-diol may be considered to be a green and clean method. This biocatalytic route yields large quantities of an enantiopure chiral building block, which is not assessable via traditional synthetic methods.

The fermentation product has seen application towards the synthesis of aminocylitols, which have been tested for their biological activity. Attempts to synthesise the fully oxygenated counterparts, cyclitols, were investigated. Expansion of previous work using a bromine substituted derivative led to a range of cross-coupled and iron co-ordinated products. Finally, a range of novel chiral acids and ketones were synthesised and evaluated for their catalytic activity towards asymmetric epoxidation.



Abbreviations

°C	Degrees Celsius
Å	Angstrom
Ac	Acetyl
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOM	Benzyloxymethyl acetal
Bt	Benzotriazole
Bu	Butyl
Bz	Benzoyl
CAN	Cerium Ammonium Nitrate
cat.	Catalytic quantity
Cbz	Carboxybenzyl
CDI	*N,N*'-Carbonyldiimidazole
Conc.	Concentrated
DCM	Dichloromethane
DIAD	Di-*iso*-propyl azodicarboxylate
DET	Diethyltartrate
DIBAL	Di-*iso*-butylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMEDA	*N,N*'-Dimethylethylenediamine
DMF	*N,N*'-Dimethylformamide
DMM	Dimethoxymethane
DMP	2,2-Dimethoxypropane
DMSO	Dimethyl sulfoxide
EDC	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDTA	Ethylene diaminetetraacetic acid
ee	Enantiomeric excess
Equiv.	Equivalents
ESI	Electrospay ionisation
Et	Ethyl
et al.	et alia
Et_2O	Diethyl ether
Et_3N	Triethylamine

EtOAc	Ethyl acetate
g	Grams
GC	Gas Chromatography
h	Hours
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HOBt	1-Hydroxybenzotriazole hydrate
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
hv	UV light
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IPA	*iso*-propyl alcohol
^{i}Pr	*iso*-propyl
LA	Lewis acid
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
m	Meta
M	Molar
m.p.	Melting point
m/z	Mass to charge ratio
*m*CPBA	*meta*-Chlorobenzoic Acid
Me	Methyl
MeCN	Acetonitrile
mg	Miligrams
MHz	Mega Hertz
mins	Minutes
mL	Milliliters
mmol	Milimoles
mol%	Molar percent
MS	Molecular Sieves
MW	Molecular weight
NBA	*N*-Bromoacetamide
*n*BuOH	*n*-Butanol
nm	nanometer
NMO	4-Methylmorpholine *N*-oxide
NOESY	Nuclear overhauser effect spectroscopy
o	*ortho*
p	*para*
PDC	Pyridinium Dichromate
Petrol	Petroleum ether

Ph	Phenyl
Piv	Pivaloyl
PMB	*para*-methoxybenzyl
*p*MBDMA	*para*-methoxybenzaldehyde dimethyl acetal
PMP	*p*ara-methoxyphenyl
ppm	Parts per million
psi	Pounds per square inch
pTSA	*para*-toluenesulfonic acid
Py	Pyridine
Quant.	Quantitative
R	Generic substrate or group
r.s.m	Recovered starting material
r.t.	Room temperature
R_f	Retention factor
TBAB	Tetrabutyl ammonium bromide
TBAF	Tetrabutyl ammonium fluoride
TBDMS	*tert* -butyldimethylsilyl
TBS	*tert* -butylsilyl
^{t}Bu	*tert* -butyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMO	Tri-methylamine *N*-oxide
TMS	Tri-methylsilyl
TPP	5,10,15,20-Tetraphenyl-21H,23H-porphine
Ts	Tosyl
V	Volts
v/v	Volume/volume
W	Watts
wt%	Weight percent
α	Alpha
β	Beta
δ	Chemical shift in parts per million
µ	Micro
µM	Micro molar
v	Wavenumber cm^{-1}

1 Introduction: Microbial Arene Oxidation

1.1 Sustainable biocatalysis [1,2]

Chemical transformations that are cleaner, more efficient, environmentally benign and cost effective are becoming ever more prevalent within the chemical industry and in research. This can be surmised by the growth in the field of green chemistry, which addresses all of these issues to ensure that chemical manufacture remains a key and prominent industry which grows and develops in a sustainable manner so that future generations can expect products for a quality of life to which we are accustomed.

Traditional synthetic methods have in most (but not all) cases their known hazards, risks and costs, associated with the process. For example most transformations require the use of volatile organic solvents, toxic and hazardous reagents, occasionally forcing reactions conditions (with the associated energy requirements) and the use of precious metals, although hopefully in catalytic amounts.

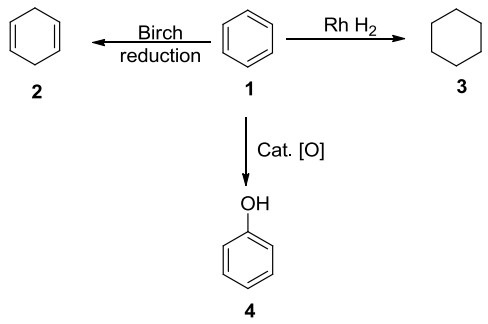
Biocatalysis is the use of an enzyme, either isolated or whole cell, which catalyses a chemical transformation. As an alternative to traditional synthesis, biocatalysis presents many benefits. Biological systems require mild reaction conditions and often produce non-toxic waste. Additionally they often proceed with very high degrees of regio–, stereo– and enantioselectivity. This selectivity is attributed to the specific size and shape of the folded proteins that make up the enzyme active site environment. As a result biocatalysis often functionalises a compound in ways which traditional chemical synthesis cannot.

Despite this biocatalysis does have its downfalls and barriers to implementation; including difficulty of enzyme isolation, necessity of co-factors, optimisation being required due to the differences between cellular and industrial setting and the need for expensive and specialised equipment which require specialised training and knowledge.

Overall, if applied correctly, biocatalysis can be viewed as a sustainable alternative to traditional synthesis.

1.2 Traditional synthetic methods which disrupt aromaticity

Selective oxidation of aromatic compounds is traditionally difficult to achieve due to the high stability of the aromatic system. Only a few synthetic methods are known to permanently disrupt this stable aromaticity, without cleaving the ring. These reactions often require harsh reaction conditions and use or produce toxic or hazardous substances, which is obviously undesirable.



Scheme 1: Reduction and oxidation of aromatic compounds.

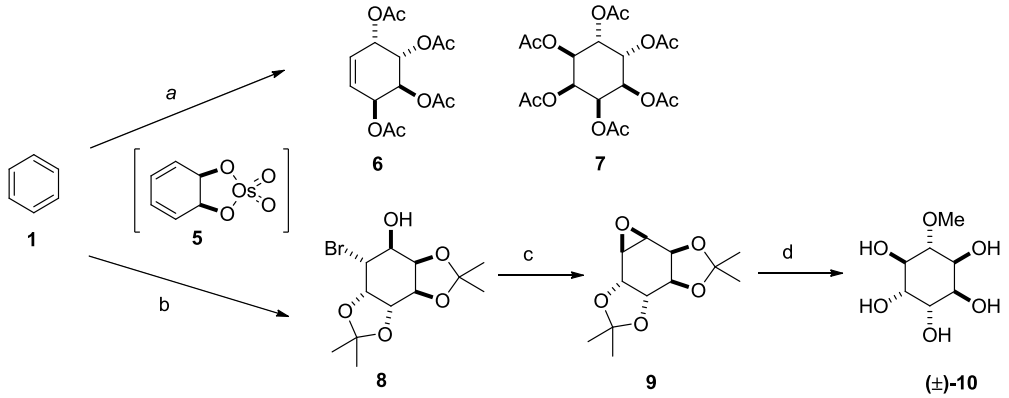
One of the few examples that demonstrates the de-aromatisation of arenes is the Birch reduction **1** → **2**.[3] This achieves the 1,4 reduction of aromatic rings to the corresponding cyclohexadienes using alkali metals (e.g. Li, Na, K) dissolved in liquid ammonia in the presence of an alcohol. However, this procedure entails undesirable hazards associated with the use of highly reactive metal reagents and toxic liquid ammonia. Scheme 1.

Recently the complete reduction of benzene has been reported with the use of a water soluble rhodium catalyst in a biphasic system **1** → **3**.[4] The work demonstrated high catalytic activity, excellent thermal stability and good catalytic recovery facilitated by the biphasic system. Scheme 1.

Many iron and other metal based catalysis are noted to be able to oxidise aromatic species,[5] however this only temporarily disrupts the aromaticity within the

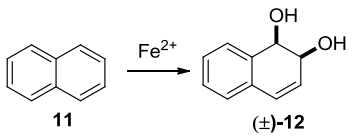
transition state of the reactions. The driving force for the completion of the reaction is often the re-aromatisation step. **1** → **4.** Scheme 1.

Perhaps the most relevant transformation relating to this project was pioneered by Motherwell in 1995. He sought a simple chemical method to produce diene diols as building blocks for biologically important molecules such as conduritols and inositols. The method involved a photochemically induced charge transfer between osmium tetroxide and benzene **1**. The presence of a suitable oxygen transfer reagent, either barium chlorate or bromate, led to formation of an osmate esters of benzene dihydrodiol **5**, which with further processing led to the synthesis of cyclitol derivatives **6** and **7**[6] and later (±)-pinitol **10**[7]. Scheme 2.



Scheme 2: Motherwell *et al.,* [6,7] Catalytic Photoinduced Charge-Transfer Osmylation.
Reagents and conditions: a) i) OsO_4 (cat.), *hv,* $Ba(ClO_3)_2$; ii) Ac_2O, Et_3N, DMAP, **6** 5%, **7** 31%; b) i) OsO_4 (cat.), *hv,* $NaBrO_3$; ii) *p*TSA, acetone, H_2O, 8%; c) K_2CO_3, MeOH, Δ, 83%; d) i)Al_2O_3, MeOH , Δ; ii) H_2O, THF, HCl, 60%.

Related to the work of Motherwell, Que *et al*. sought a bio-inspired catalyst to mimic the oxidation of aromatic compounds by bacteria **11** → **12**. Insertion of the diol moiety breaks the aromaticity of the naphthalene starting material. This is the only known chemical example which mimics a bacterial transformation of the type with which this thesis is concerned and has helped to further the understanding of the role of the iron centre present in the enzymes that carry out these oxidative transformations. [8,9] Scheme 3.

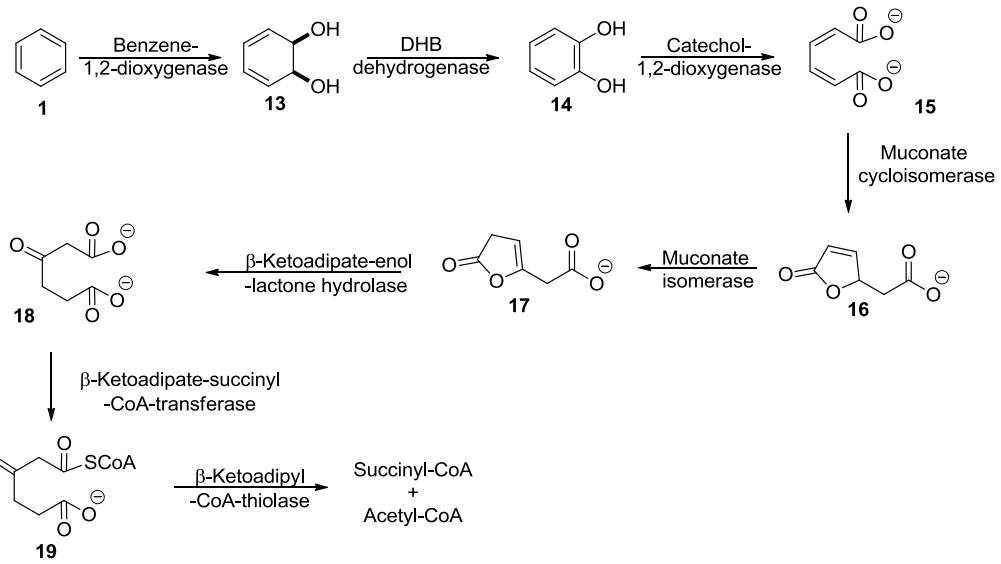


Scheme 3: Que *et al.,*[8,9] Catalyst = $[Fe^{II}(TPA)(NCMe)_2]^{2+}$ TPA = tris(2-pyridylmethyl)-amine)

1.3 Microbial arene oxidation (MAO)

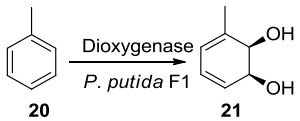
As highlighted above, disrupting the aromaticity is difficult to achieve via traditional synthetic means. A recent review in 2011 highlighted the importance of dearomatisation strategies in the synthesis of complex natural products. This review noted the importance of microbial arene oxidation (MAO) as a viable alternative to traditional synthetic methods, and detailed its use in synthesis. [10]

Microbial arene oxidations are performed by bacteria which contain dioxygenase enzymes. Dioxygenase enzymes are known to occur within certain soil bacteria which have the ability to metabolise and mineralise aromatic compounds. The full degradation pathway of aromatic compounds by this class of bacteria is shown below. [11] Scheme 4.



Scheme 4: Benzene degradation pathway

Mutant strains of the bacterium containing the dioxygenase enzyme which are blocked in the DHB (1,2-dihydro-1,2-dihydroxybenzoate) pathway accumulate and excrete the *cis*-diol **13**, which can be isolated and used in synthesis.[12] Scheme 4.



Scheme 5: Transformation of toluene with *Pseudomonas putida* F1

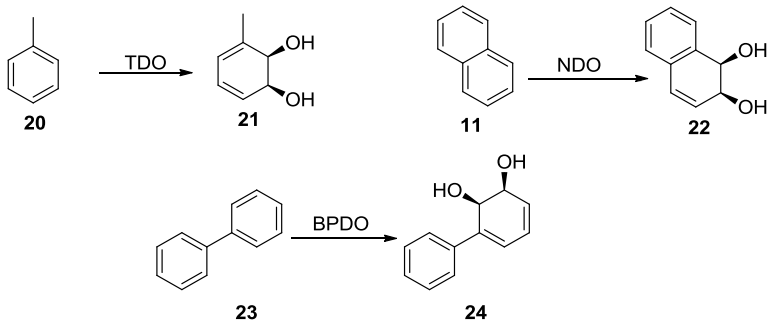
This transformation was first reported by Gibson in 1968, who successfully isolated and identified the *cis*-dihydrodiol product **21** from the oxidation of toluene **20** with

P. putida F1. Scheme 5.[13] Since the time of Gibson the area of microbial arene oxidation has seen rapid expansion, today over 400 arene *cis*-diol products have been reported and their use and application to synthesis is vast. [2,12,14]

1.4 Classes of microbial arene oxidation

1.4.1 Common classes of microbial arene oxidation

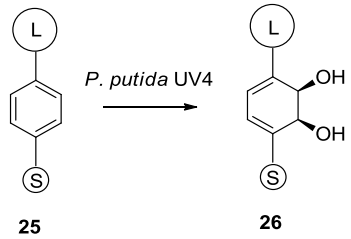
Many different microorganisms, including naturally occurring, mutant and genetically modified recombinant strains have been reported to contain dioxygenase enzymes which can carry out MAO. These dioxygenase enzymes are classified due to their substrate specificity. The vast majority of organisms express toluene dioxygenase (TDO) **20** – **21**, other significant classes include naphthalene dioxygenase (NDO) **11** – **22** and biphenyldioxygenase (BPDO) **23** – **24**. Scheme 6. These classes of enzyme are not as tightly defined as the term suggests as in many cases there is no such specificity and several enzymes act on a number of different substrates.



Scheme 6: Microbial arene oxidation classes

Nevertheless these transformations are well understood and reliable predictive models have been developed for these enzyme classes. The transformations are known to occur with high levels of regio– and stereospecificity. Boyd *et al.,*[15] investigated the dihydroxylation of a variety of 1,4-disubstituted benzenes, **25**, and measured and compared their associated enantioselectivities of the corresponding diols, **26**. Their conclusions led to a predictive model for the observed enantioselectivities based on the size of either substituent. If L>S high enantioselectivities are observed and a single *cis*-diol enantiomer is obtained. In contrast if L≈S (e.g. L = F, S = H) enantioselectivities dramatically decrease. He

concluded that size of the substituents was a dominant factor in the selection of which bond is preferentially oxidized. Scheme 7.

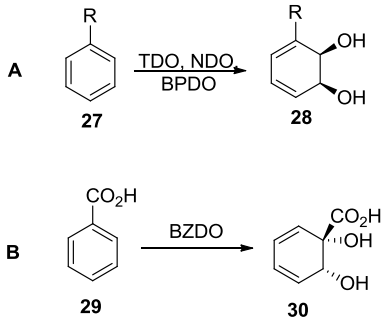


Scheme 7: Boyd's model for size and selectivity of dihydroxylation products. [15]

Possible problems with the use of mutant strains of the dioxygenase enzyme is that the blocked DHB dioxygenase pathway, which allows for the accumulation of the desired *cis*-diol product, may become reactivated if the bacteria is stressed and may need to metabolise the *cis*-diol for energy. The use of recombinant dioxygenase expression in *Escherichia coli* prevents the reactivation of DHB dioxygenase, as it is no longer present. TDO, the most commonly used dioxygenase enzyme has been readily expressed in *E. coli* over a number of different generations and mutations. The use of *E. coli* enables faster turnover and greater stability in the production of the microbial oxidation product.[16]

1.4.2 Less common MAO class: Benzoate Dioxygenase (BZDO)

An example of a less common class of microbial arene oxidation enzyme is that of benzoate dioxygenase **29** → **30.** In comparison to the more common classes of dioxygenase as described above, the BZDO dioxygenase enzyme displays not only different regioselectivity but the opposite sense of enantio-induction. e.g. the substrate is oxidised *ipso*, *ortho* as shown in **B** as opposed to *ortho, meta* as shown by **A**. Scheme 8.



Scheme 8: Benzoate dioxygenase transformation.

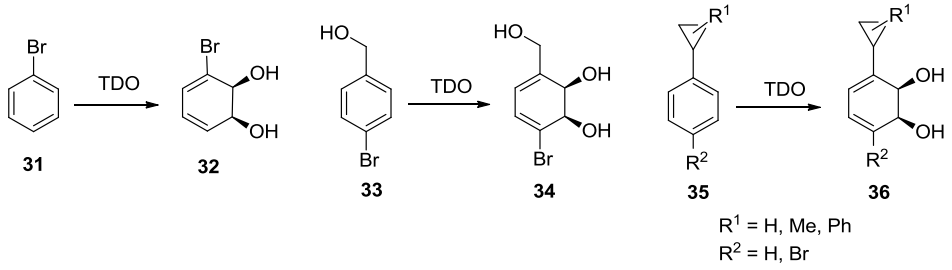
There are few BZDO containing bacteria prevalent in the literature, the most commonly reported strains include *Ralstonia eutropha* B9[17], *P. putida* U103[18] and *P. putida* KTSY01[19].

Oxidation of benzoic acid by bacteria was first reported in 1948.[20] Not until 1971 did Reiner and Hegeman first report the breakdown of benzoic acid by a mutant strain of bacteria, *R. eutropha* B9 (formerly *Alcaligenes eutrophus*), blocked in the DHB dioxygenase pathway, and isolate diene *cis*-dihydrodiol **30**. Scheme 8B.[21]

This chemical oxidation of benzoic acid is considered to be a unique transformation as there is no equivalent in synthesis for the insertion of a *cis*-diol of *ipso*-*ortho* substitution pattern to benzoic acid.[16]

1.4.3 Halogenated substituents in MAO

A common substrate utilised in TDO dihydroxylation is bromo benzene **31,** giving **32**. Beneficially, the bromine acts as a synthetic handle to further functionalise the compound. The presence of the bromine does not reduce the activity of the enzyme. Other substituted benzenes have also been used in TDO containing bacteria to widen the substrate and synthetic scope **33 – 36**.[22-25] When there is more than one substituent present enantioselectivities decrease as is the case with **34** which presents a 20% *ee*. This is expected as per Boyds predictive models, which states with similar size substituents results in a reduction in observed enantioselectivities.[15,22,23] Scheme 9.

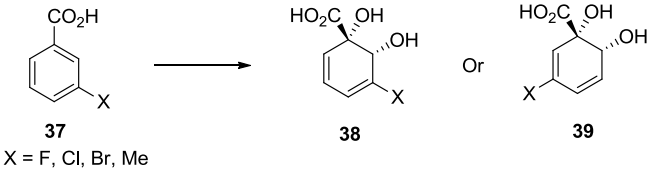


Scheme 9: Substrate scope within TDO

As shown above, TDO can tolerate a variety of substituents on the aromatic ring and hence shows great versatility in organic synthesis. In contrast BZDO shows little tolerance to aromatic substituents and therefore has less broad synthetic scope.

There is very little work on the use of substituted benzoates in MAO. In all cases work is focused on halogenated benzoates. In consideration of the possible

oxidation products of *meta*-substituted benzoate, it has been suggested that two possible products could exist, **38** and **39.** These arise due to the different orientation of the substrate within the enzyme active site. Scheme 10.



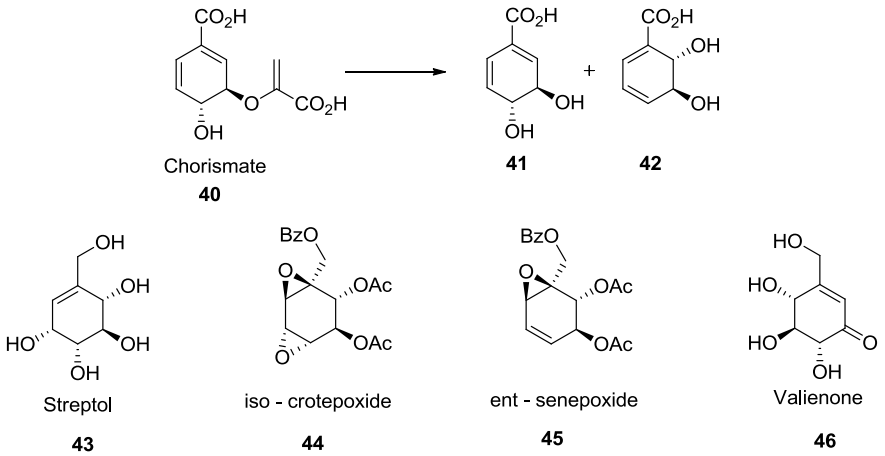
Scheme 10: Two possible products 3- and 5- substituted *cis*-diols.

There is little consistency within the literature with regards to the preference for formation of either the 3- **38** or the 5- **39** substituted *cis*-diols, though it has been suggested that electron withdrawing and bulky substituents both reduced the rate of the biotransformation. This suggests that both steric and electronic effects are involved in the rate determining step. [13,21,26-28]

(More detailed literature on halogenated substrates in BZDO can be found at the start of Chapter 3, where it finds relevance to the results of the bromobenzoic acid MAO product being exploited in synthesis.)

1.5 Other diols available from bacteria

We have seen above, that microbial arene oxidation produces *cis*-diols. Access to the biologically derived *trans*-diol is not so straightforward [29] and has been the significant work of Müller *et al.* This work utilises the biologically derived chorismate **40**. It was found that chorismate could be subjected to further biological transformation using a mutant strain of *Klebsiella,*[30] and later recombinant *E. coli.*[31] This enabled production of *trans*-diols **41 – 42** on a large scale (up to 15 gL^{-1}).



Scheme 11: Use of *trans*-diol in synthesis

The synthetic potential for these substrates was realised as the building blocks for carbohydrate and cyclitol synthesis, as demonstrated in the synthesis of plant growth inhibitor streptol **43**,[31] biologically active epoxides crotepoxide **44** and senepoide **45**[32] as well as valienone **46**[33].

Scheme 11.

1.6 Examples in synthesis

Dihydrodiol metabolites produced from bacteria, offer a range of functionalities which have the possibility to be manipulated further into synthetically and biologically interesting complex molecules.

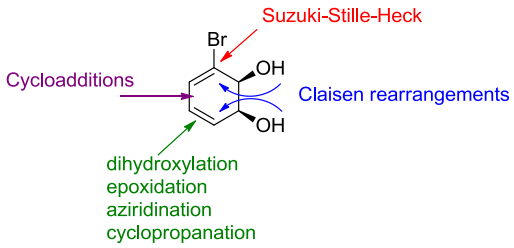


Figure 1: Synthetic utility of dihydrodiols.

Some of these synthetic handles have been highlighted. Figure 1. This next section describes some key examples where *cis*-diol compounds have been utilised in synthesis.

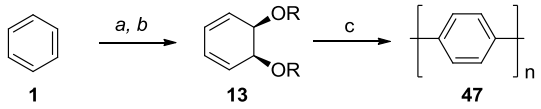
There is a large abundance of organic synthesis research publications which showcase the use of microbial arene oxidation in synthesis. The majority of works utilise TDO enzymes which have been expressed in *E. coli* for ease of use and stability.

This section includes a brief overview of the historical examples of MAO in synthesis and further discusses the targeted synthesis of cyclitols, inositols, aminocarbasugars, carbasugars and other natural products.

1.6.1 Historical perspective

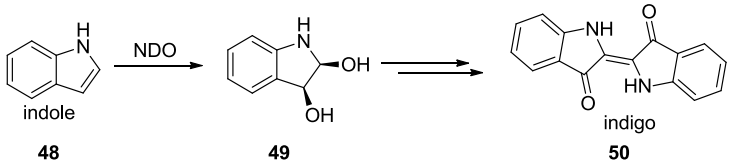
It was not until 20 years after Gibson[13] first identified and assigned the stereochemistry of the enzymatic dihydroxylation products that synthetic applications were found: The earliest known example of microbial arene oxidation in synthesis dates back to 1983, where ICI (Imperial Chemical Companies)

developed the use of *cis*-dihydrodiol **13** in the synthesis of polyphenylene **47**. [34,35] Scheme 12.



Scheme 12: Synthesis of polyphenylene from benzene via microbial arene oxidation. Reagents and conditions: a) *P. putida;* b) Ac_2O, Py; c) Radical initiator then Δ.

The continued work of Gibson *et al.* in 1983 exploited NDO in the synthesis of indigo **50**, [36] which was later optimised and scaled up as an industrial process. [37] Scheme 13.



Scheme 13: Synthesis of indigo

1.6.2 Cyclitols

Cyclitols are polyhydroxy-substituted cycloalkanes with at least three hydroxy groups, each attached to a different ring carbon atom. Many naturally occurring cyclitols are biologically active and hence are interesting targets for organic synthesis.

Ley and co-workers in 1987 was first to realise the potential of the possible products from microbial arene oxidation in the synthesis of cyclitols. They synthesised a series of highly oxygenated structures: (+) and (–)-pinitol **51**, [38] (+)-conduritol-F **52**, *myo*-inositol and *myo*-inositol-1,4,5-triphosphate **53**.[39] Figure 2.

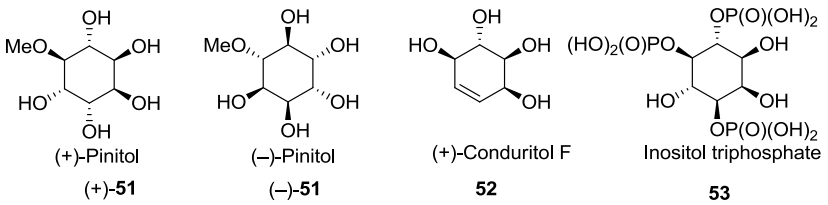
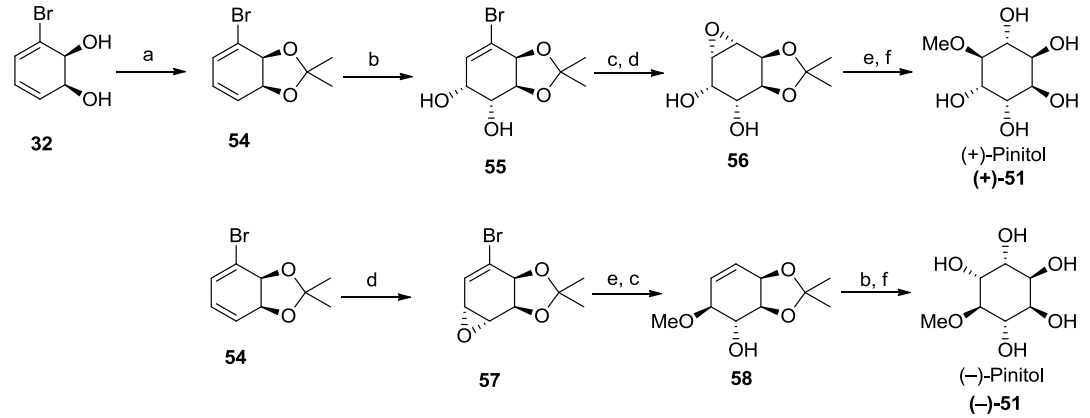


Figure 2: Cyclitols, Ley's work

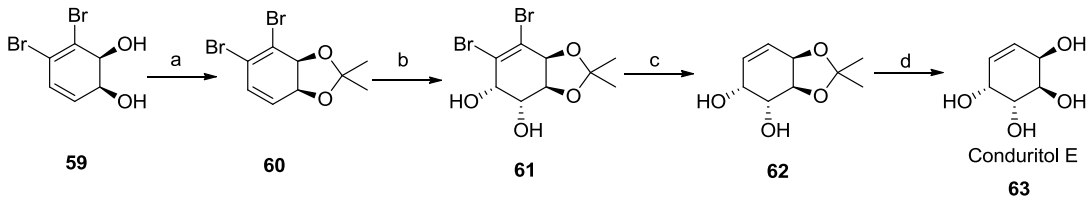
Further elaborating on Ley's original work, Hudlicky designed an enantio-divergent synthesis of both enantiomers of pinitol **51**.[40] Scheme 14. This utilises the plane of symmetry present in either enantiomer. Using identical reagents but changing their

order of addition allowed the two enantiomers to be synthesised from the same starting material. Enantio-divergent synthesis has been employed in the synthesis of many other cyclitols, carbohydrates and other natural products with latent planes of symmetry.[41]



Scheme 14: Hudlicky 1990 [40] enantio-divergent synthesis of pinitol. Reagents and conditions: a) DMP, *p*TSA, acetone, quantitative; b) OsO_4, NMO, H_2O, acetone, 85%; c) $LiAlH_4$, THF, 85%; d) *m*CPBA, CH_2Cl_2, 86%; e) MeOH, Al_2O_3, 90%; f) HCl, H_2O, acetone.

Later Hudlicky in 2006 also synthesised (–)-conduritol E **63**, from di-bromo benzene **59**. Scheme 15.[42] Conduritols are a class of cyclitols which contain a derivative double bond, and four hydroxyl groups. There are six possible isomeric forms, all of which have been synthesised via microbial arene oxidation.[43]



Scheme 15: Hudlicky 1996 [42] synthesis of (–)-conduritol E. Reagents and conditions: a) DMP, *p*TSA, acetone, 95%; b) OsO_4, NMO, H_2O, acetone, 71%; c) nBu_3SnH, AIBN, THF, 64%; d) HCl, MeOH, 81%.

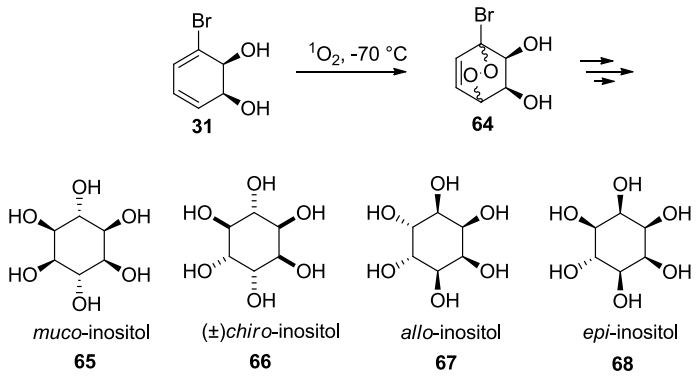
There are many noted advantages of the use of *cis*-diols in cyclitol synthesis.[43] Firstly MAO offers substrates in high yields and high enantiomeric purities while providing the six carbon skeleton of the targeted compounds. The double bonds are easily oxygenated via epoxidation or dihydroxylation methods to the desired cyclitols. Additionally synthesis is often enantio-divergent, as demonstrated by Hudlicky in 1990, allowing access to both enantiomers.[44]

1.6.3 Inositols

Inositols are structures which consist of a cyclohexane core substituted with six hydroxy groups. This gives rise to six contiguous stereocentres, the arrangement of which gives rise to nine possible stereoisomers.[45]

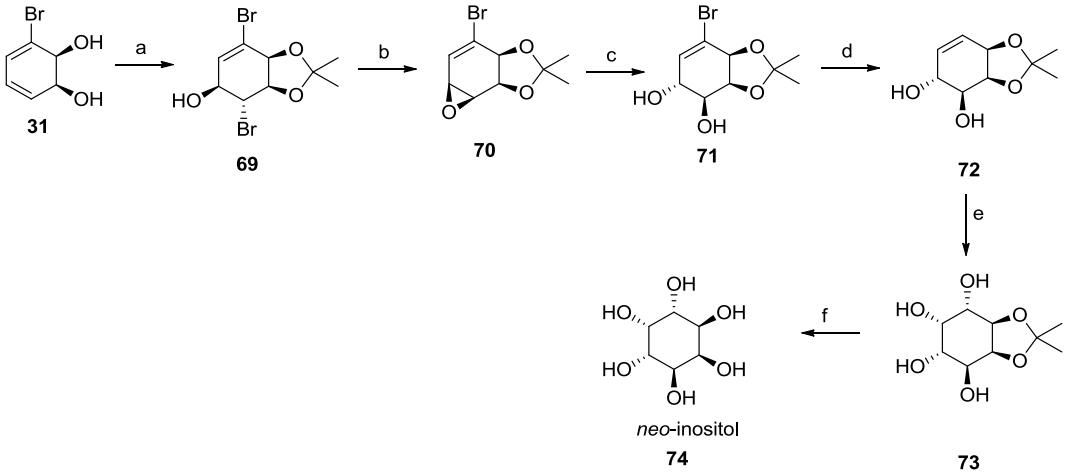
Chemists have extensively studied inositols, due to their important biological application including as glycosidase inhibitors, for intercellular communication, protein anchoring and phosphate storage.[46] Traditional synthetic techniques require transformation of simple carbohydrates or oxidation of alkenic compounds, but this can be difficult. Microbial arene oxidation offers a technique to give high levels of selectivity in the synthesis.[43]

Carless in 1993 reported synthesis of *muco-, chiro-, allo-* and *epi-* inositol **65 – 68** from *meso*-diol **31**. The work utilised photo-oxidation with singlet oxygen to obtain an endo peroxide bridge **64**. Scheme 16. [47]



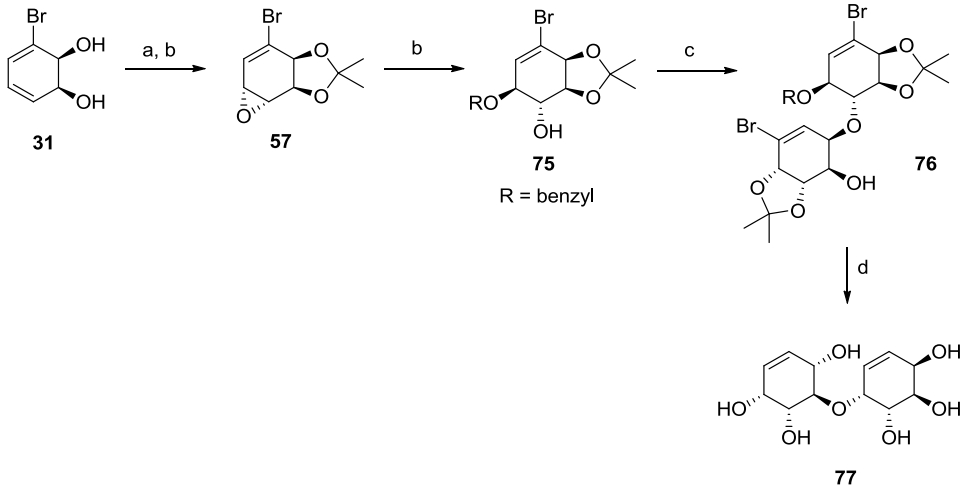
Scheme 16: Careless 1993, use of singlet oxygen in inositol synthesis.

Subsequent work from Hudlicky 1993 – 2000 [48,49] synthesised *neo, (+)-chiro, muco, allo* and *myo-* inositol from products of microbial oxidation, using similar methods and reagents. A more recent publication details the synthesis of *neo*-inositol **74** in a 17% overall yield over six steps without need for chromographic purification of any of the intermediate compounds.[50] Scheme 17.



Scheme 17: Inositols from microbial arene oxidation.[50] Reagents and conditions: a) DMP, *p*TSA, acetone; then 1,3-dibromo-5,5-dimethylhydantoin, H_2O, acetone; b) 10% aq KOH, DME; c) r.t., to Δ; d) Bu_3SnH, AIBN, benzene, Δ; e) OsO_4, NMO, ^tBuOH, acetone-H_2O, f) conc. HCl, MeOH.

Further application of MAO to inositol targets has seen bromo-diene **31** used in the targeted synthesis of oligomers of conduritol-F and *muco*-inositol, which were synthesised and evaluated for their glycosidase inhibition.[51] Here alcohol **75** was used as a nucleophile to couple with epoxide **57** to form an oligomer. Final conduritol-F oligomer **77** was obtained via electrochemical dehalogenation of **76**.[52] Scheme 18.



Scheme 18: Conduritol-F from MAO as a glycosidase inhibitor[51] Reagents and conditions: a) DMP, *p*TSA, acetone; b) *m*CPBA, CH_2Cl_2, 75% 2 steps; c) **57,** $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 55%; d) -3.0 V, Et_4NBr, MeCN; then TFA:THF:H_2O (4:1:1), 40%.

1.6.4 Aminocyclitols

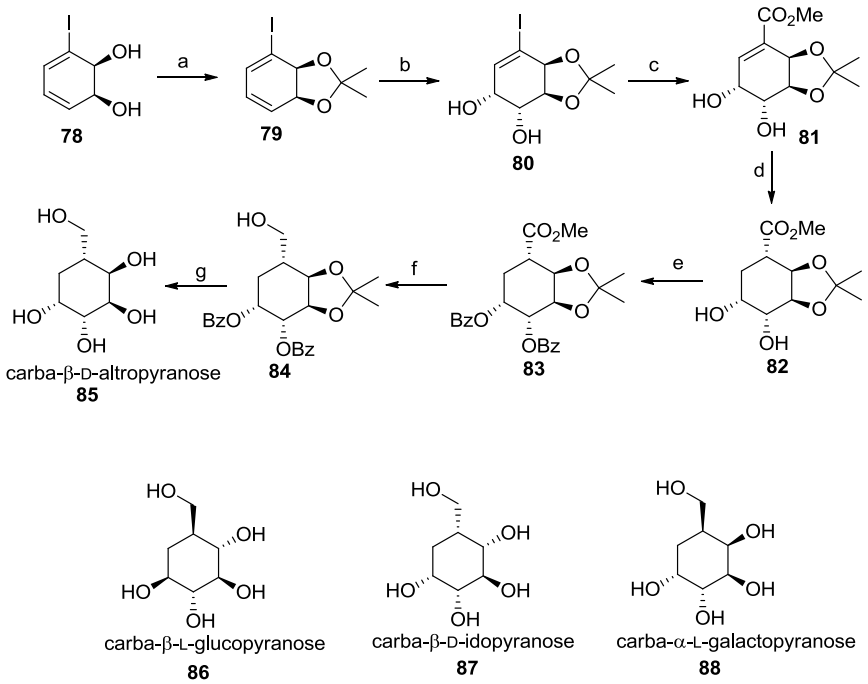
Aminocyclitols pose structural similarities to that of a variety of antibiotics, glycosidase inhibitors and other biologically active molecules, and as such they prove important synthetic targets for chemists. Aminocyclitols are cycloalkanes containing at least one free or substituted amino group and three additional hydroxyl groups on the ring atoms. Because of their structural similarity, aminocyclitols are often referred to as aminocarbasugars.[53]

We have seen that microbial arene oxidation has been applied to cyclitols, conduritols and inositols, expansion is therefore straightforward to similar amine analogues.

(This area is reviewed in detail at the beginning of Chapter 2: Aminocyclitols)

1.6.5 Carbasugar derivatives

Pseudo sugars or carbasugars also have potential biological activity and can act as glycosisdase inhibitors.[54] These are usually synthesised from naturally occurring sugars or metabolites from plants or bacteria on small scales.



Scheme 19: Boyd sugar derivative work[55] Reagents and conditions: a) DMP, *p*TSA, 98%; b) OsO_4, NMO, acetone, H_2O, 87%; c) $Pd(OAc)_2$, CO, NaOAc, MeOH, 81%; d) Rh/Al_2O_3, H_2; e) BzCl, Py, 28% 2 steps; f) $LiAlH_4$, 74%; g) TFA, 90%.

Scheme 19 highlights an example of how *cis*-diols have been used to synthesise several sugar analogues **85 – 88**. It is worth nothing that in these examples the

seventh sugar carbon had to be added onto the six carbon framework of the microbial oxidation product, **80** – **81**, it would be more step and atom efficient if the microbial oxidation product already contained the seven carbon framework.

1.6.6 Natural product synthesis

The aminocyclitol motif is found in many natural products for example the amaryllidaceae group of alkaloids e.g. pancratistatin **89**, narciclasine **90** and lycoricidine **91**. These have antimicrobial activity against mycobacteria as well as possessing anti-tumour and glycosidase inhibition. Again these have been synthesised via routes employing microbial arene oxidation. Figure 3.[56-58]

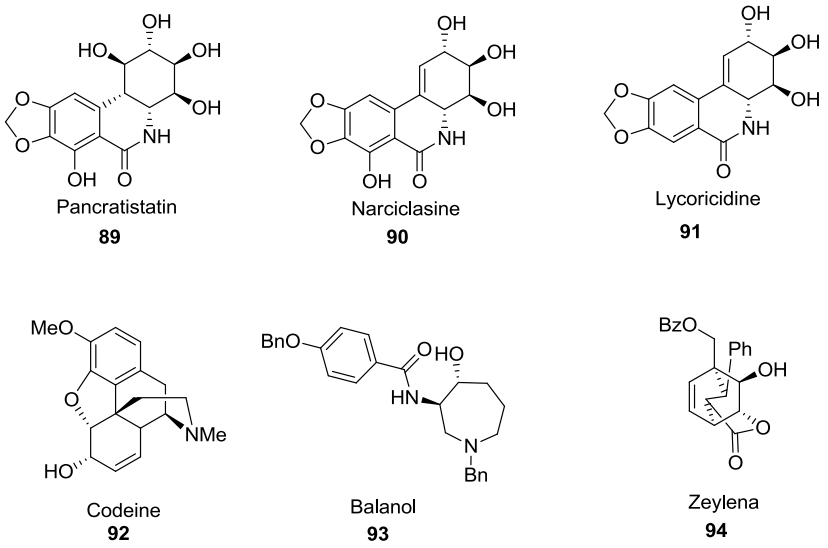


Figure 3: Natural Product Synthesis

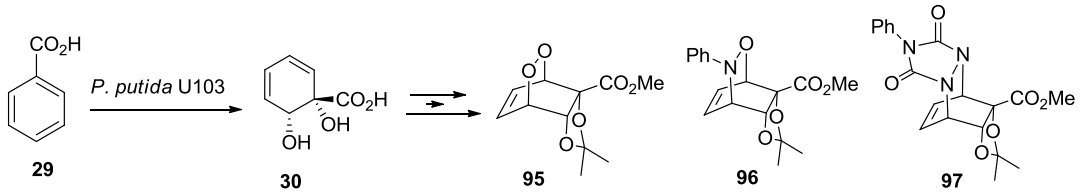
Other natural products synthesised from microbial arene oxidation include codeine **92**,[41,59] balanol **93** a protein kinase C inhibitor[60] and Zeylena **94**[61] a structurally interesting natural product. Figure 3.

1.7 Benzoate dioxygenase in synthesis

BZDO has seen few uses in synthesis, there are notably fewer examples of BZDO in current literature (i.e. only ≈15 examples as of 2013) than the more common TDO, NDO and BPDO.

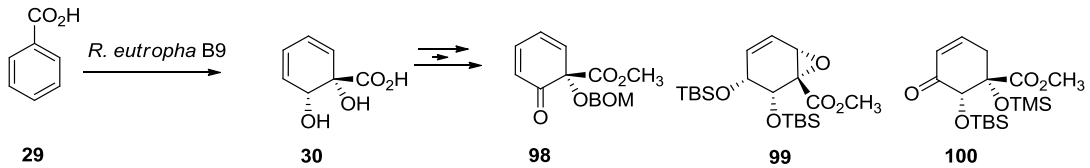
Widdowson in 1995, reported the first example of BZDO used in synthesis. Scheme 20.

The work utilised *P. putida* U103 as a source of BZDO, in an attempt to determine the absolute stereochemistry of the MAO product. As well as describing 1*S,* 2*R* stereochemistry of the diol by synthesis of a crystalline derivative, the work also sets precedent for [4 + 2] cycloadditions with peroxide **95**, nitroso **96** and urazole **97** dienophiles. The work observed *syn* addition of the dienophile in the presence of the free diol dienes (attributed to a favourable interaction between the diol and approaching dienophile). In contrast, when the diol was protected as an acetonide, the opposite selectivity was observed and the dienophile added in an *anti* fashion. This was attributed to an unfavourable steric clash between approaching dienophile and bulky acetonide group.[18]



Scheme 20: Widdowson 1995.[18]

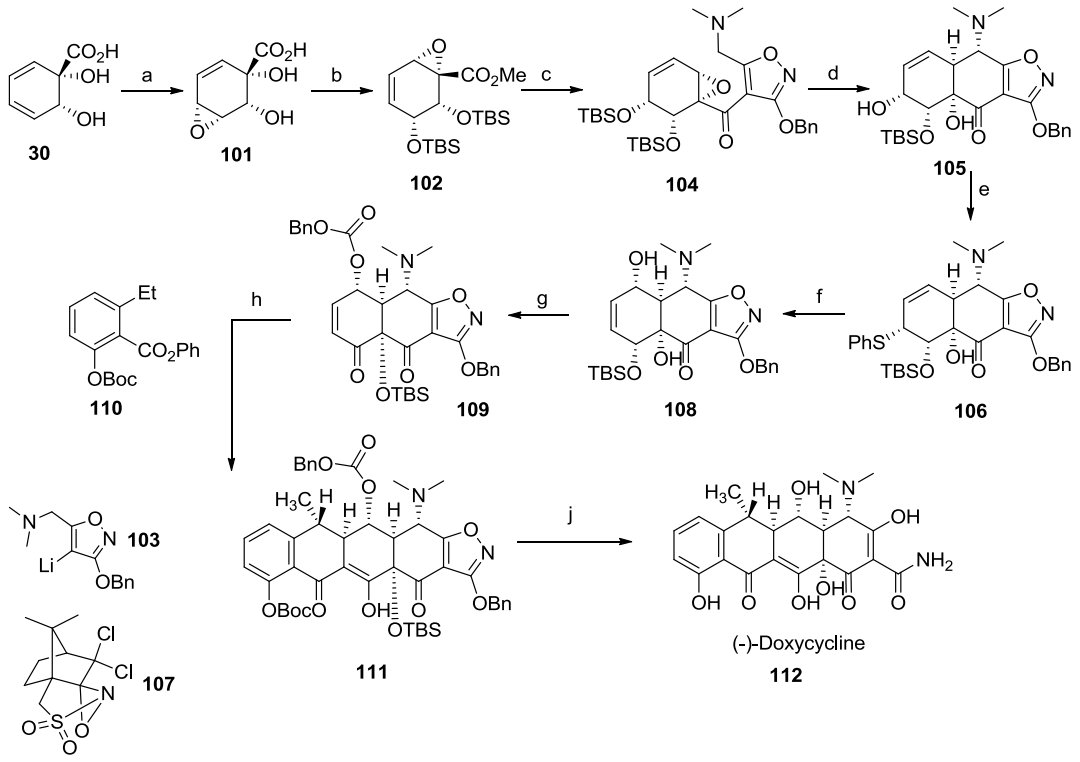
Not until 2001 did Myers *et al*. realise the synthetic potential of substrates derived from the *cis*-dihydrodiol **30**. The work created a library of 16 novel compounds that could be used as chiral building blocks in organic synthesis, e.g. **98** – **100**. Scheme 21. The work demonstrated the synthetic utility and robustness of the substrate **30** under different reaction conditions. Additionally the work also described large scale preparation of the *cis*-diol acid **30**, allowing for the process to become more accessible to the everyday chemist, who may be unfamiliar with biological techniques and processes.[17]



Scheme 21: Myers work[17]

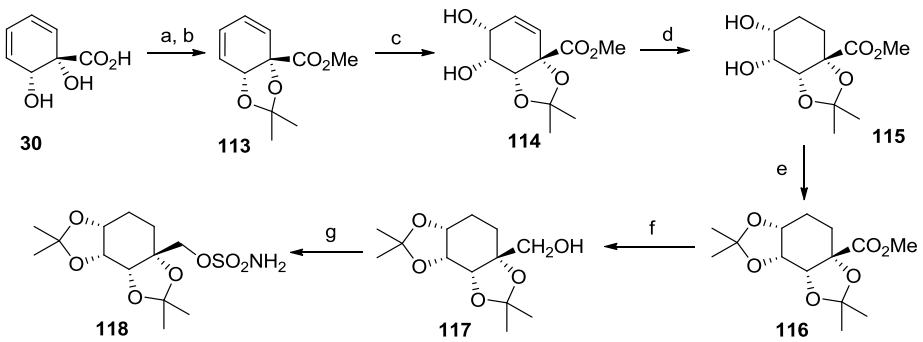
Later work by Myers, 2005, developed total syntheses of unnatural deoxycycline **112**[62] antibiotic from the product of microbial arene oxidation in which all of the

stereocentres were installed under substrate control from the initial benzoate *cis*-diol **30**. Scheme 22.



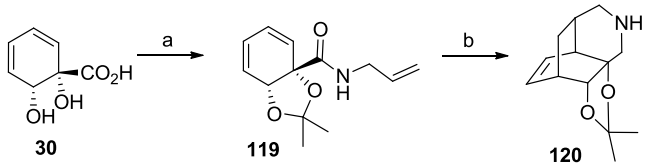
Scheme 22: Myers' antibiotics.[62] Reagents and conditions: a) *m*CPBA, EtOAc, 83%; b) i) $TMSCHN_2$; ii) TBSOTf, Et_3N, 70%; c) THF, -78 °C, organolithium reagent **103**, 73%; d) i) LiOTf, $PhCH_3$, 60 °C; ii) TFA, CH_2Cl_2, 62%; e) i) CBr_4, PPh_3; ii) PhSH, Et_3N, 87%; f) i) chiral oxidant **107**; ii) $P(OMe)_3$, MeOH, 70 °C, 76%; g) i)BnO_2CCl, DMAP; ii) TBAF, HOAc; iii) IBX, DMSO; iv) TBSOTf, Et_3N 85%; h) LDA, TMEDA, THF, -78 °C, **109**, -78 °C - 0 °C, 79%; j) i) HF, MeCN; ii) H_2, Pd, THF, MeOH, 90%.

In 2004 Parker *et al.* reported the synthesis of a series of Topiramate analogues such as **118**, a novel anticonvulsant, in only seven steps from microbial oxidation product **30**. This highlighted the synthetic utility of the compounds described by Myers in 2001. The paper also describes the use of **30** to synthesise carba-β-L-fructopyranose, a carbohydrate target.[63] Scheme 23.



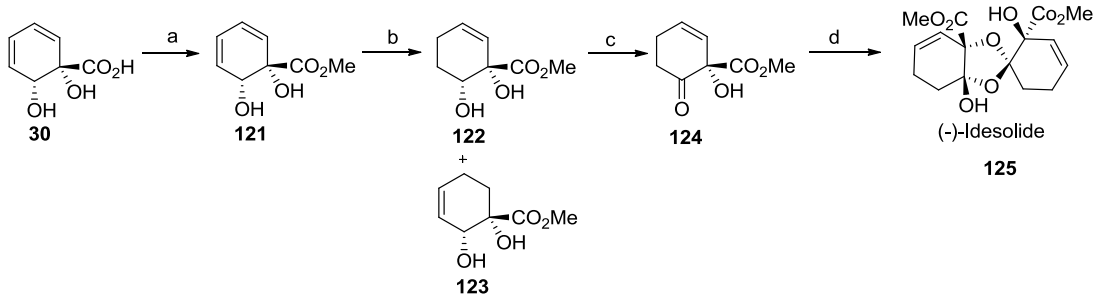
Scheme 23: Parker *et al.* [63] Reagents and conditions: a) $TMSCHN_2$, MeOH, C_6H_6, 96%; b) DMP, HCl, acetone, 98%; c) OsO_4, NMO, *t*-BuOH, H_2O, acetone, 73%; d) H_2 Pd/C, EtOAc, 95%; e) DMP, HCl, acetone, 80%; f) DIBAL-H, THF, 85%; g) $ClSO_2NH_2$, NaH, DMF, 93%.

Mihovilovic[64,65] with access to *R. eutropha* B9 concentrated on intramolecular Diels–Alder reactions using tethered dieneophiles under microwave conditions to produce product **120**. Scheme 24.



Scheme 24: Mihovilovic 2004, 2010. Reagents and conditions: a) i) DMP, *p*TSA, acetone, 94%; ii) EDC, HOBt, Et_3N, allylamine, DCM, 83%; b) Microwave 210 °C, 500 min, 28%.

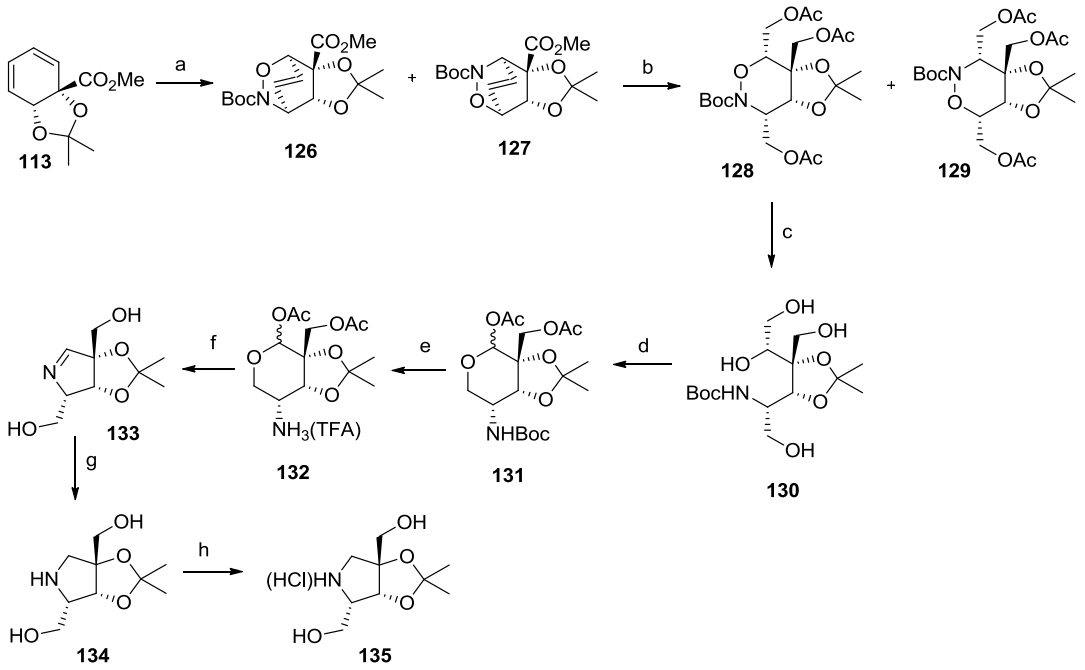
Recent work from Hudlicky in 2011, synthesised the dimeric natural product Idesolide **125** in only 4 steps from the microbial oxidation product **30**.[66] The synthetic procedure involved diimide reduction of diene **121** to form a regioselective mixture of alkenes **122** and **123** in a 2:1 ratio, of which **122** was isolated and oxidised to ketone **124.** Dimerisation of **124** was eventually achieved with Na_2HCO_3 to give (–)-idesolide **125** in a 19 % overall yield. This work again reiterates the possible ease of fast and efficient synthesis from MAO products. Scheme 25.



Scheme 25: Hudlicky 2011.[66] Reagents and conditions: a) CH_2N_2, THF, 0 °C, 79%; b) Potassium azodicarboxylate, AcOH, MeOH, 0 °C, 61%; c) IBX, DMSO, 60%; d) $NaHCO_3$, 66%.

The most recent work this year from Hudlicky[67] exploited the *ipso, ortho* diene **30** for the targeted synthesis of hydroxylated pyrrolidines **135**. Polyhydroxylated pyrrolidines are interested targets as this structural motif arises in many biologically active molecules and natural products. Hudlicky's synthesis utilised hetero Diels–Alder methodology through to regioisomers **126** and **127**. Ozonolysis and subsequent reduction of the ozonide and acylation gave separable isoxazolidine

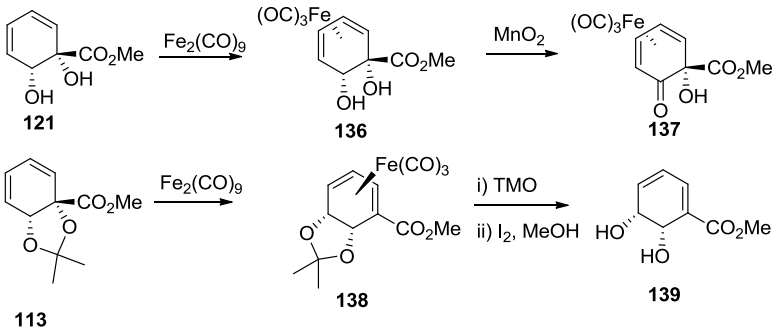
acetates **128** and **129**. Hydrolysis and immediate N-O bond reduction with $Mo(CO)_6$ gave tetrol **130**. Oxidative cleavage and acylation gave *bis* acetate **131**. Removal of the Boc protecting group with TFA to furnished the stable salt, which under basic hydrolysis conditions gave pyrroline **133**. Finally hydrogenation and salt formation gave final pyrrolidine **1375** Scheme 26.



Scheme 26: Hudlicky[67] Pyrrolidines. Reagents and conditions: a) BocNHOH, $NaIO_4$, MeOH, H_2O, 96%; b) i) O_3, CH_2Cl_2, -78 °C, $NaBH_4$; ii) Ac_2O, 22%; c) i) K_2CO_3, MeOH; ii) $Mo(CO)_6$, MeCN, H_2O, 87%; d) i) SiO_2, $NaIO_4$, CH_2Cl_2, 0 °C; ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 56%; e) TFA, CH_2Cl_2, 62%; f) K_2CO_3, MeOH, 81%; g) Pd/C, H_2, AcOH, H_2O, quant; h) MeOH, HCl, 40 °C, 75%.

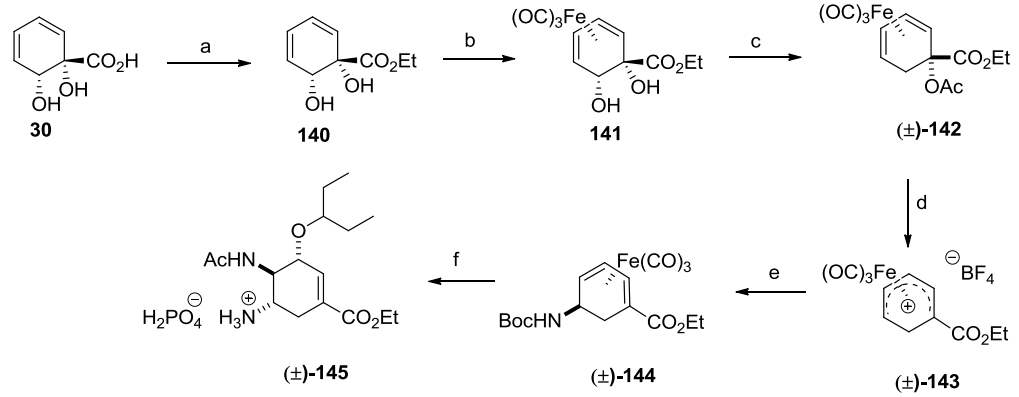
1.8 Work originating from the Lewis group

Much of the work within the Lewis group 2010 – 2013 has centred on the use of the benzoate *cis*-dihydrodiol **30**. Work by Ali-Khan *et al.* [68,69] has concentrated on the use of tricarbonyliron(0) co-ordination in order to stabilise or protect the diene moiety to obtain structures which would not be accessible with the uncomplexed diene, such as synthesis of compound **137** from **136**. Scheme 27. Later work investigated the facial selectivity of the iron co-ordination and found that when the diol was protected as an acetonide **113**, co-ordination of the metal to the upper face led to unexpected rearrangement of the acetonide **138**. Following the removal of the iron an arene *cis* diol with a different substitution could be obtained, **139**, being *ortho, meta* substituted, similar to that obtained with TDO *but the opposite enantiomer*.



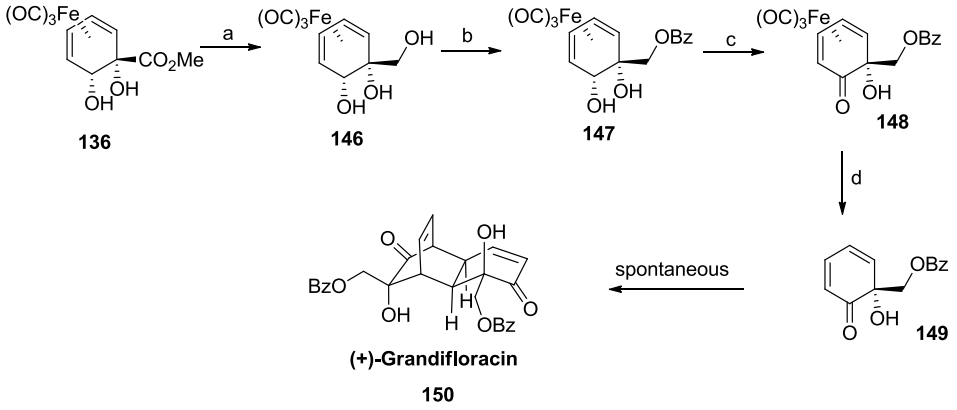
Scheme 27: Ali-Khan *et al.*

Most recently Ali-Khan utilised iron complexation towards a known intermediate in the synthesis of Oseltamivir (Tamiflu®) **145**. This work exploits many [η^5] cationic complexes and susceptibility to nucleophilic addition to obtain a wide library of synthetic intermediates. Scheme 28.



Scheme 28: Ali-Khan[63,70] Reagents and conditions: a) EtI, CsF, DMF, 23 h, 69%; b) [$Fe_2(CO)_9$], THF, 5 d, 61%; c) i) HBF_4, Ac_2O. ii) $NaBH_4$, 18 h, MeCN, 0 °C, 39%; d) HBF_4, CH_2Cl_2, 100%; e) *i*Pr_2NEt, *t*$BuOCONH_2$, CH_2Cl_2, 24 h 82%; f) ref [71].

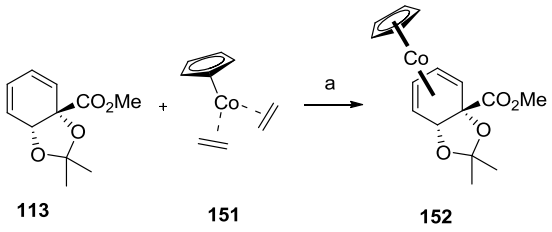
Within the Lewis group use of these iron complexes has seen application to the synthesis of the natural product (+)-grandifloracin **150**. Scheme 29. [72]



Scheme 29: Grandifloracin synthesis.[72] Reagents and conditions: a) DIBAL-H, THF/CH_2Cl_2, -78 °C; b) BzCl, 2,4,6-collidine, THF, 33% (2 steps); c) MnO_2, CH_2Cl_2, 78%; d) CAN, acetone, 34%.

At the time of this publication, (–)-grandifloracin had been isolated from nature, but its absolute configuration was not known. The final material synthesised in this study was (+)-grandifloracin **150**, and therefore assumed that at the time this material was not the natural product. However, further publications have also identified and isolated (+)-grandifloracin **150** from a natural source, suggesting both enantiomers are natural products. Furthermore, the (+)-grandifloracin **150** has since been found to be a potent antiausterity agent against human pancreatic cancer cells.[73]

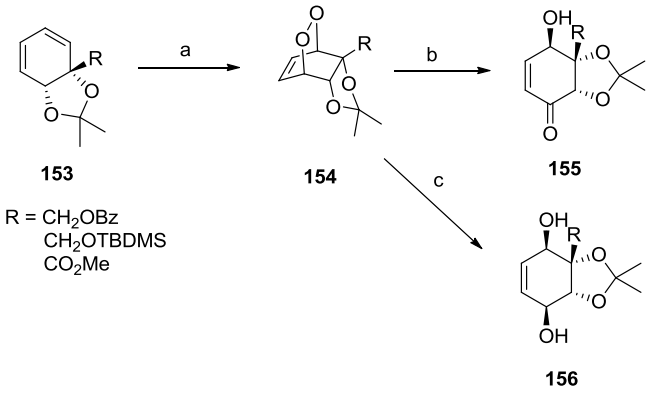
Expanding on the topic of metal complexation to *ipso, ortho* diene **30**, diverging away from the use of iron; Cobalt complexes were investigated **152**.[74] This brief report highlights the viability of cobalt co-ordination to MAO products with synthetic applications yet to be scoped. Scheme 30.



Scheme 30: Cobalt complex of MAO product.[74] Reagents and conditions: a) PhMe, r.t., 30 mins, 26% after recrystallisation.

Natural products have been targeted in the total synthesis of zeylenols and zeylenones structures from the *ipso, ortho* diene **153.** [75] This work utilises singlet oxygen methodology to reach a series of natural products, highlighting novel

Kornblum–DeLaMare rearrangement via neighbouring group participation through to targeted structures **154 – 156**. Scheme 31. (This work has significant relevance to Chapter 3: Cyclitols).



Scheme 31: Synthesis of zeylenols via photooxygenation.[75] Reagents and conditions: a) O_2, TPP, CCl_4, 12 h, 10°C, 81-90%; b) *i*Pr_2NEt, CH_2Cl_2, 94-100%; c) thiourea, CH_2Cl_2/MeOH, r.t., 12 h, 63-99%.

Additional work has targeted compounds with potential biological activity. Structurally similar compounds are known glycosidase inhibitors used for treatment of diabetes. In particular three aminocarbasugars **157 – 159**, were synthesised and tested. However these compounds showed no biological activity. Figure 4.[76]

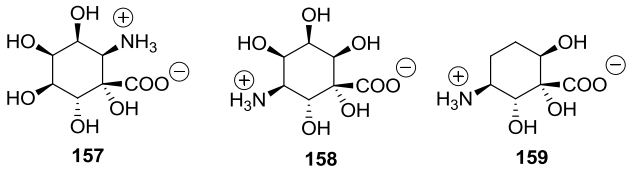
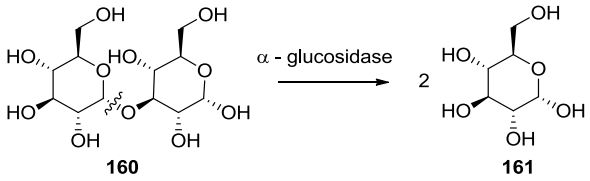


Figure 4: Aminocarbasugar synthesis

1.9 Glycosidase inhibitors

As shown above by the numerous synthetic examples a common application of MAO products is the synthesis of natural products which possess biological activity, notably glycosidase inhibition. This section describes in detail that application.

Glycosidases are enzymes that catalyse the cleavage of glycosidic bonds in oligosaccharides and glycoconjugates **160 – 161**. Scheme 32.[54] Glycosidases are fundamental to several biological processes including digestion, metabolism as well as immune response, intercellular recognition, cellular differentiation and solubility of proteins etc.[77]



Scheme 32: Glycosidase enzyme function

The two types of glycosidase, α and β, each hydrolyse the corresponding forms of the sugar, depending on the stereochemistry of the hydroxyl group at the anomeric position. Figure 5.

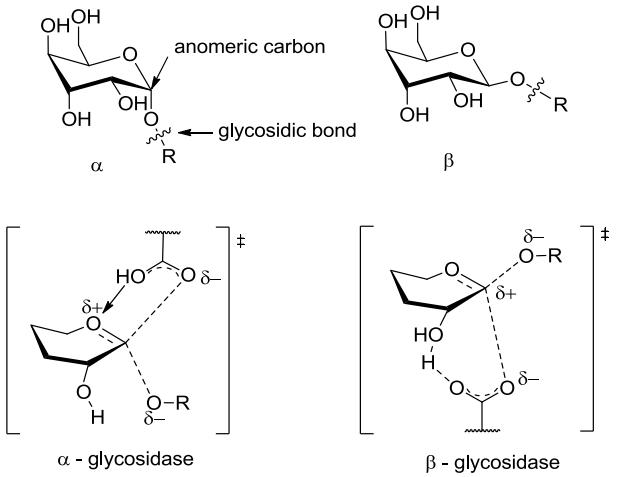
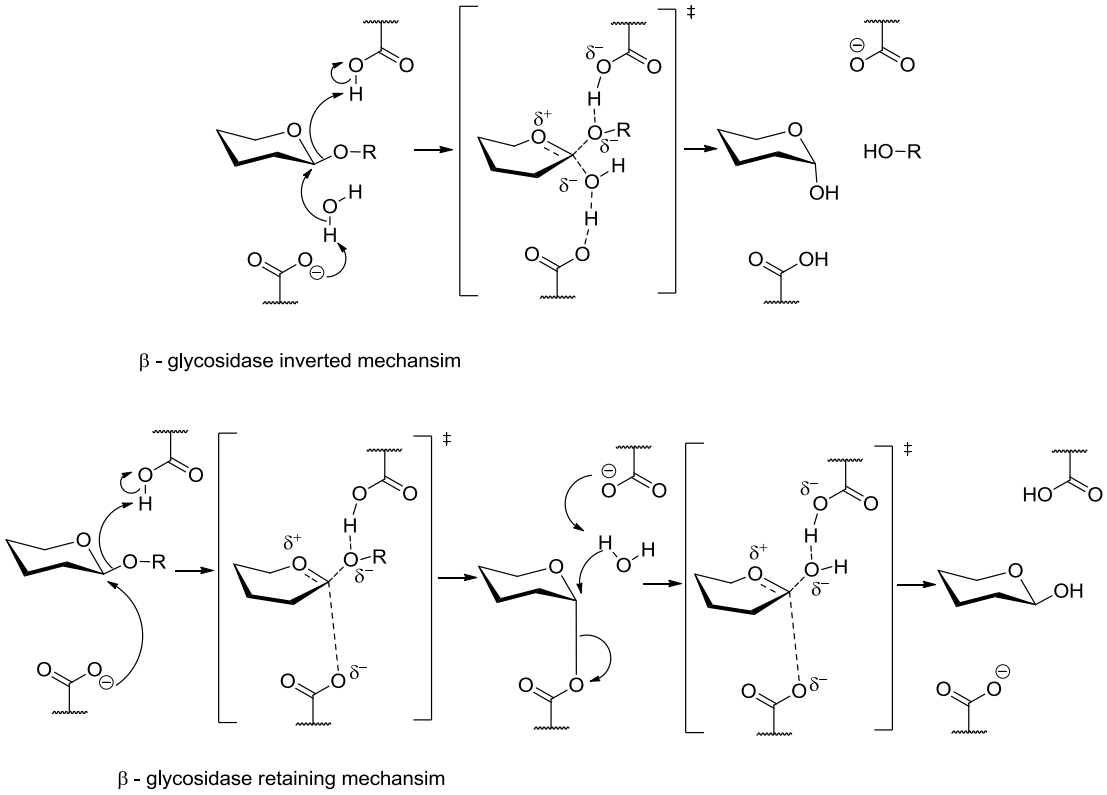


Figure 5: α and β glycosidases and their transition states

The mechanism of the breakdown of sugars by glycosidase involves a key transition state. Figure 5.[54] The intermediates of both α and β glycosidase react via slightly different transition states depending on the position of the anomeric hydroxyl group. In both transition states there is a *syn* relationship between the attacking nucleophilic oxygen from the carboxyl group and the anomeric carbon. In the α case, the other carboxyl oxygen interacts directly with the endocyclic oxygen developing a oxocarbenium like transition state. In comparison with the β case the remaining carboxy oxygen interacts with the hydroxyl group at C2, favouring carbocation formation.

Furthermore both α and β glycosidase can act via two distinctive mechanisms; either resulting in inversion or retention of the cleaved glycosidic bond. Below is an example of both β glycosidase mechanisms. Scheme 33. Both involve oxacarbenium-ion-like transition states and a pair of carboxylic acids at the active site.



Scheme 33: β-glycosidase mechanisms. Inversion and retention.

In the case of the inversion mechanism, the reaction is completed in a single step and via a single transition state structure. The acidic enzyme residues have to be approximately 10 Å apart in order to fit both the substrate and the water molecule into the enzymatic cavity.

In contrast, the retaining glycosidase proceeds via a two-step process; first via the enzyme being glycosylated which forms an intermediate, which is then broken down by nucleophilic water in the deglycosidation step. In this case the enzyme residues are approximately 5.5 Å apart.[78,79]

Common glycosidase inhibitors both natural and synthetic include disaccharides, iminosugars, carbasugars and thiosugars. Glycosidase inhibitors interact with their targets by mimicing this transition state, hence rendering it either inactive or less efficient at metabolising carbohydrates. Glycosidase inhibitors have many potential medical applications, and have been studied as HIV agents and treatments for diabetes, obesity, glycosphingolipid lysosomal storage disease and cancers.

Commercial glycosidase inhibitors include acarbose (Precose®) **162**, voglibose (Basen®) **163**, miglitol (Glyset®) **164** and *N*-butyl-1-deoxynojirimycin (Zavesca®) **165**. Figure 6. **162 – 164** are used in the treatment for non-insulin dependent, type II, diabetes. These drugs act to reduce postprandial hyperglycemia by interfering with the digestion of carbohydrates. While **165** is employed for the control of Gaucher's disease, which relates to disturbed lysosomal storage.

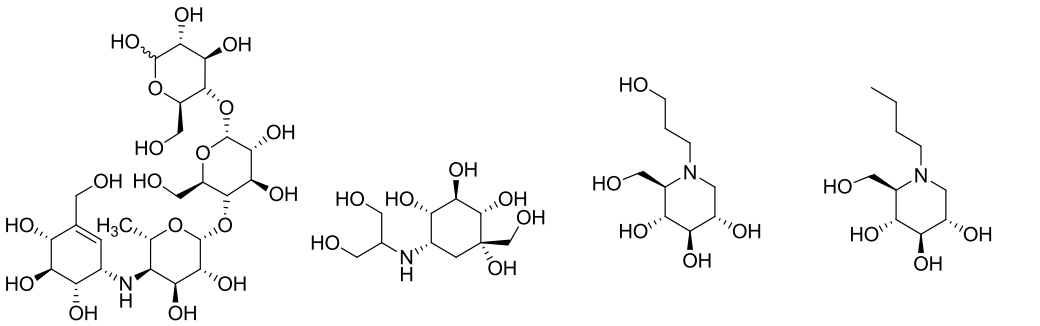


Figure 6: commercially available glycosidase inhibitors.

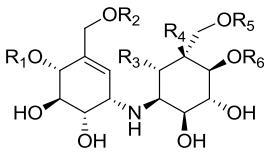
Concentrating on carba and pseudoamino sugars, these are of great structural interest as the cyclic oxygen is replaced with a carbon, which is similar enough in structure to fit into the enzymatic site, but does not induce the same level of electronic effects as seen in the transition states described above. Additionally the presence of a basic nitrogen attached to the ring has been shown to increase the hydrophobic interaction within the enzyme pocket. [54]

Carbasugars and aminocarbasugars therefore have great potential as glycosidase inhibitors, and if synthesised via MAO this could potentially provide sustainable routes to biologically active compounds.

2 Chapter 2: Aminocyclitols

2.1 Introduction

Aminocyclitols are poly-hydroxylated cycloalkanes containing at least one free or substituted amino group. Aminocyclitols are an interesting class of compounds which can serve as effective mimics of natural carbohydrates; this similarity is acknowledged in their alternative name of aminocarbasugars.[1] The amino functionality is fundamental in affecting the biological activity, and lack of the endocyclic oxygen leads to enhanced hydrolytic stability.[1 2] Several aminocylitols possess structural similarities to a variety of antibodies,[80] glycosidase inhibitors[81] and other biologically active molecules, and as such they prove important synthetic targets for chemists. Natural aminocylitols include antibiotics such as validamycins **166**. Table 1.[82,83] Simpler aminocylitols of the inosamine **167** class are found in several natural products which display antibiotic characteristics.[83] Notably a few aminocyclitols are currently in clinical use; e.g. acarbose **162**,[84] Voglibose **163**,[85] miglitol **164** [81] (technically an aminosugar, not azacarbasugar) which are α-glycosidase inhibitors that are used in the treatment of type II diabetes.[86] Figure 7.



Validamycins

166

Validamycin	R_1	R_2	R_3	R_4	R_5	R_6
A	H	H	β-D-Glc	H	H	H
B	H	H	β-D-Glc	H	OH	H
C	H	α-D-Glc	β-D-Glc	H	H	H
D	H	H	H	H	H	α-D-Glc
E	H	H	α-D-Glc(1-4)-β-D-Glc	H	H	H
F	α-D-Glc	H	β-D-Glc	H	H	H
G	H	H	β-D-Glc	OH	H	H
H	H	H	α-D-Glc(1-4) -β-D-Glc	H	H	H

Table 1: Validamycin R groups

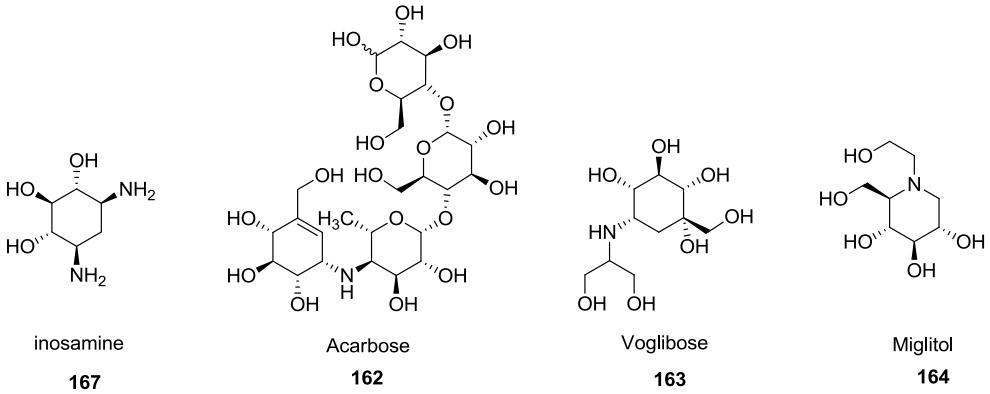
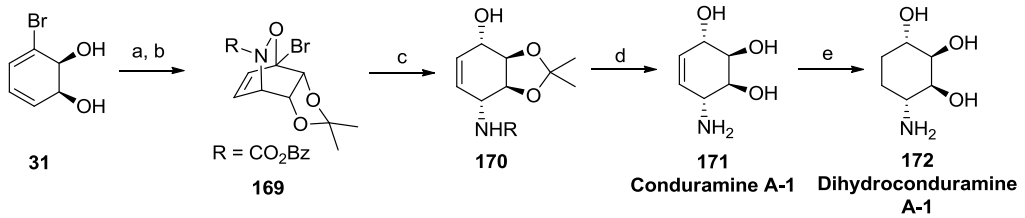


Figure 7: Natural and commercially available aminocyclitols

2.1.1 Aminocyclitols from MAO

The application of MAO towards the formation of a variety of cyclic, poly-hydroxylated and complex structures including cyclitols, conduritols and inositols has been discussed previously in the introduction. Expansion is therefore straightforward to similar amine analogues; aminocyclitols.

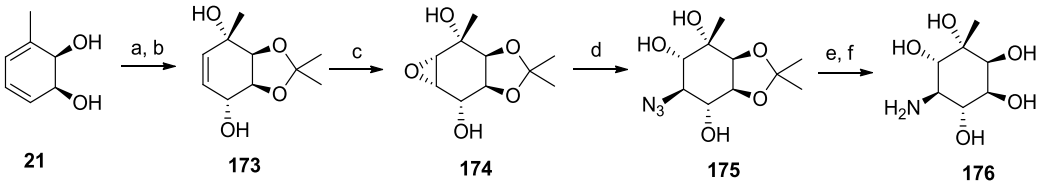
The significant difference lies in the chemical procedures utilised to insert the nitrogen functionality into this class of compound. This is most often achieved via a hetero-Diels-Alder (HDA) approach, as in Hudlicky 1991, synthesis of Conduramine A-1 **171**.[87] Addition of benzyl-*N*-hydroxycarbamate to $BuNIO_4$ generates the reactive acylnitroso *in situ* which adds to the diene with complete regioselectivity. Reductive cleavage of the N-O bond and further transformation gave conduramine **171** in a 24% overall yield. Scheme 34.



Scheme 34: Hudlicky Conduramine A-1 Synthesis. Reagents and Conditions: a) DMP, acetone, *p*TsOH, 95%; b) nBu_4NIO_4, benzyl-*N*-hydroxycarbamate, 52%; c) Al/Hg, THF/H_2O, 91%; d) AcOH, THF/H_2O, 99%; e) H_2, Pd/C, MeOH, 54%.

An alternative method of nitrogen insertion involves alkene epoxidation followed by ring opening with a nitrogen nucleophile e.g. azide,[88] phthalimide,[89] ammonia[90] or other amines.[91] An example from Carless[92] utilises the dihydrodiol MAO product of

toluene from *P.putida* **21***.* Photooxidation and epoxidation inserts the oxygen functionality stereospecifically due to substrate control. The azide attacks regioselectively to form **175** followed by reduction and deprotection to give aminocyclitol **176** in 18% yield over 6 steps form the MAO product. Scheme 35.

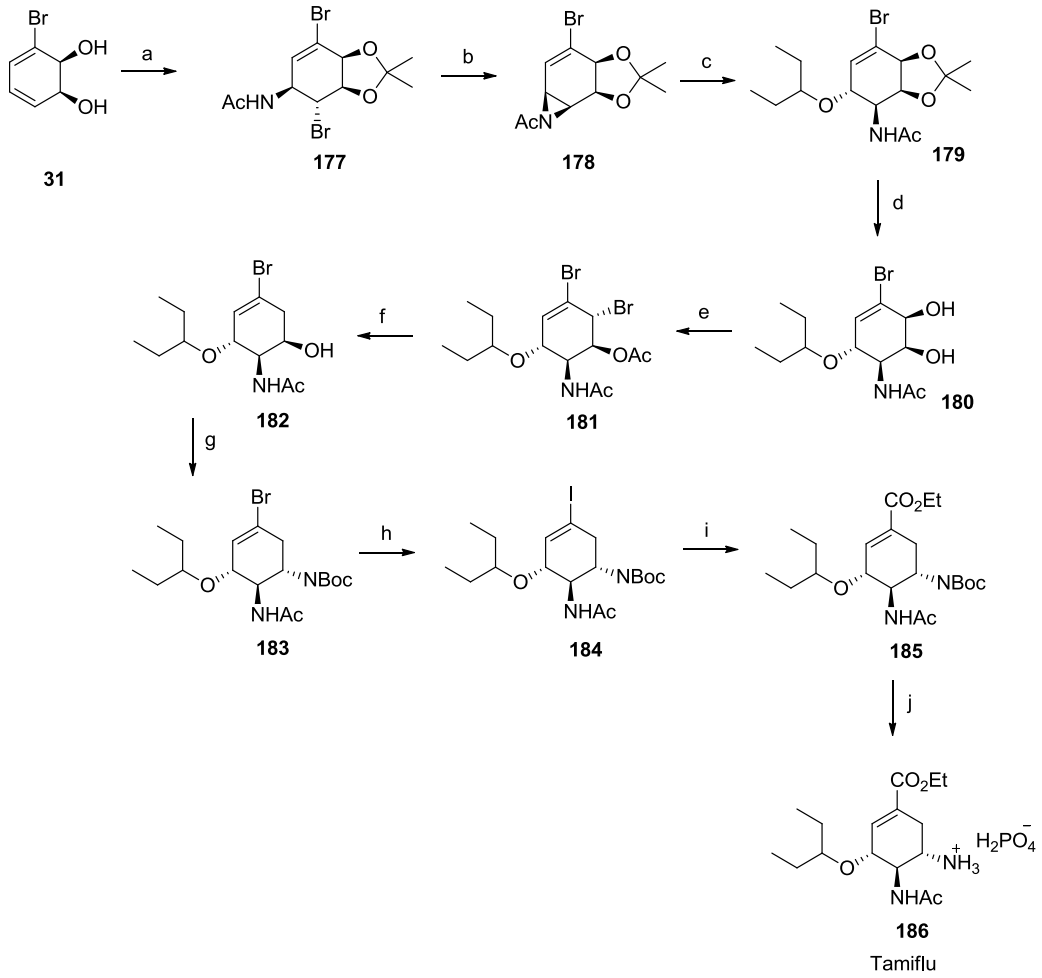


Scheme 35: Carless aminocyclitol sysnthesis azide nitrogen insertion.[92] Reagents and Conditions: a) O_2, methylene blue, *hv*; then thiourea, MeOH, 18 h, 53%; b) DMP, acetone, TsOH, 92%; c) *m*CPBA, CH_2Cl_2, 2 days, 61%; d) DMF, H_2O (20:1), NaN_3, reflux, 20 h, 71%; e) AcOH, H_2O (1:9), 80°C, 1 h, 96%; f) H_2, Pt, 50 psi, EtOH, 4 h, 92%.

2.1.2 Tamiflu

An interesting example of an amine-containing bioactive product is that of oseltamivir, or Tamiflu®. The current industrial synthesis relies on the availability of naturally occurring pure shikimic acid which can be problematic, additionally the process utilises an azide reagent, which on a large industrial scale can present a risk of explosion.[93] Several different methods have been used to synthesise Tamiflu without using shikimic acid, [94] herein we describe approaches which utilize MAO derived 1,2 *cis*–dihydrodiols.

The first from 2008, Fang *et al.*[93] started with commercially available bromo *cis*–dihydrodiol **31** transformed regio– and stereoselectively via bromo-acetamidation to **177**. This was converted to the aziridine **178** which was ring opened with 3-pentanol to give **179**. Bromination gave **181** which was reduced using super hydride $LiBHEt_3$ to alcohol **182**. This was converted to the carbamate via the isocyanate to give **183**, avoiding the previous azide route. Subsequent coupling reactions to convert the side chains gave the desired Tamiflu product **186**. Scheme 36.

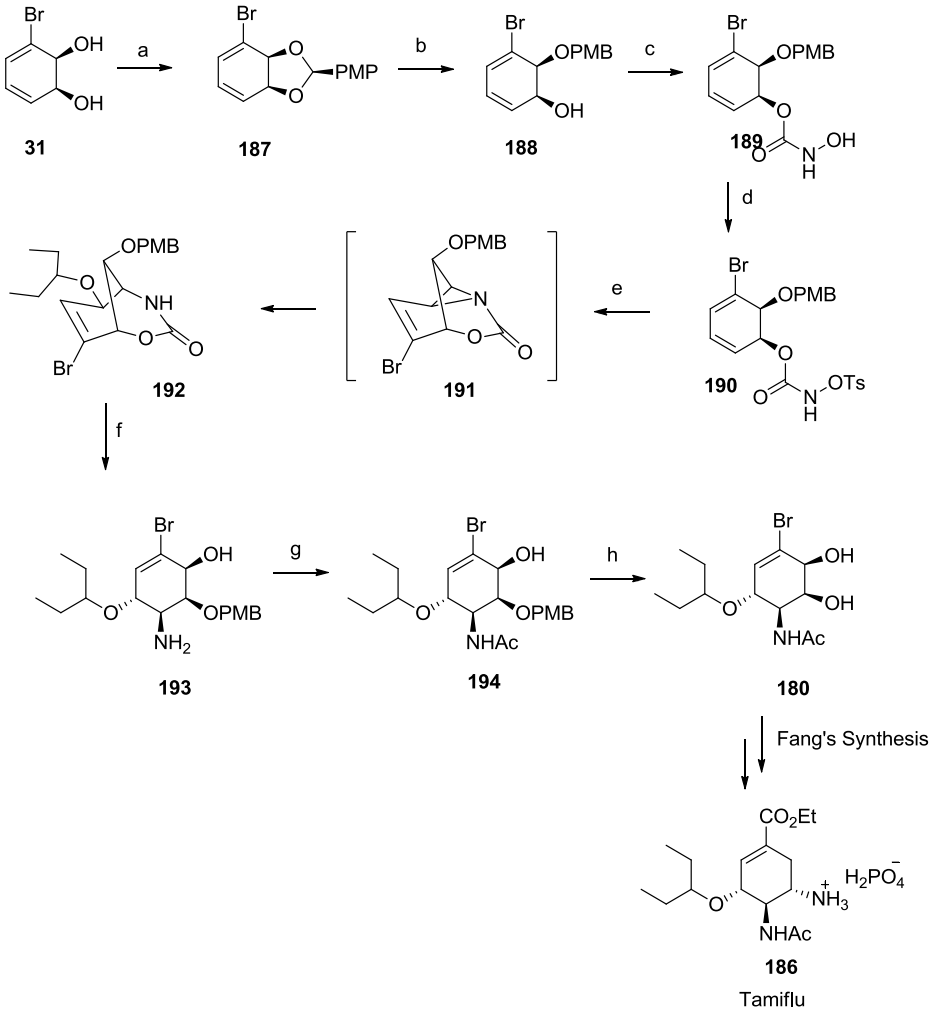


Scheme 36: Fang Synthesis of Tamiflu.[93] Reagents and Conditions: a) i) DMP, acetone, cat. H^+, 0 °C to r.t., 0.5 h; ii) cat. $SnBr_4$, NBA, H_2O, CH_3CN, 0 °C, 0.5 h, 75% 2 steps; b) LHMDS, THF -10 °C to 0 °C, 0.5 h; c) 3-pentanol, $BF_3{\cdot}OEt_2$, -10 °C to 0 °C, 6 h, 73% 2 steps; d) conc. HCl, MeOH, 50 °C, 6 h, 94%; e) $AcOCMe_2COBr$, THF, 0 °C to r.t., 3.5 h; f) $LiBHEt_3$, THF, 0 °C to r.t., 2 h, 82% 2 steps; g) DDQ, PPh_3, $n$$Bu_4NOCN$, CH_3CN, r.t., 18 h, then tBuOH, Δ, 24 h, 78%; h) CuI, DMEDA, nBuOH, 120 °C, 24 h; i) cat. $[Pd(OAc)_2]$, CO, NaOAc, EtOH, r.t., 24 h, 82% 2 steps; j) H_3PO_4, EtOH, 50 °C, 6 h, 81%.

In summary Fang provides an azide free route presenting good yields, 26% over 11 steps, from the commercially available MAO bromo *cis*-dihydrodiol. Described as hazardous and toxic free, utilising simple procedures Fang intends to work towards a large scale synthesis.[93]

Banwell *et al.*[95,96] in 2008 developed upon Fang's synthesis providing a route to key intermediate **180**, again utilising the MAO derived bromo *cis*-dihydrodiol **31**. Banwell sought to use the copper catalysed intramolecular aziridiation[97] to afford a cyclic carbamate intermediate **192**, formed through 3-pentanol ring opening of acylaziridine **191**. Subsequent basic hydrolysis ring opening of the carbamate,

acylation, and acid deprotection of the PMB group gave intermediate **180** from Fang's synthesis.

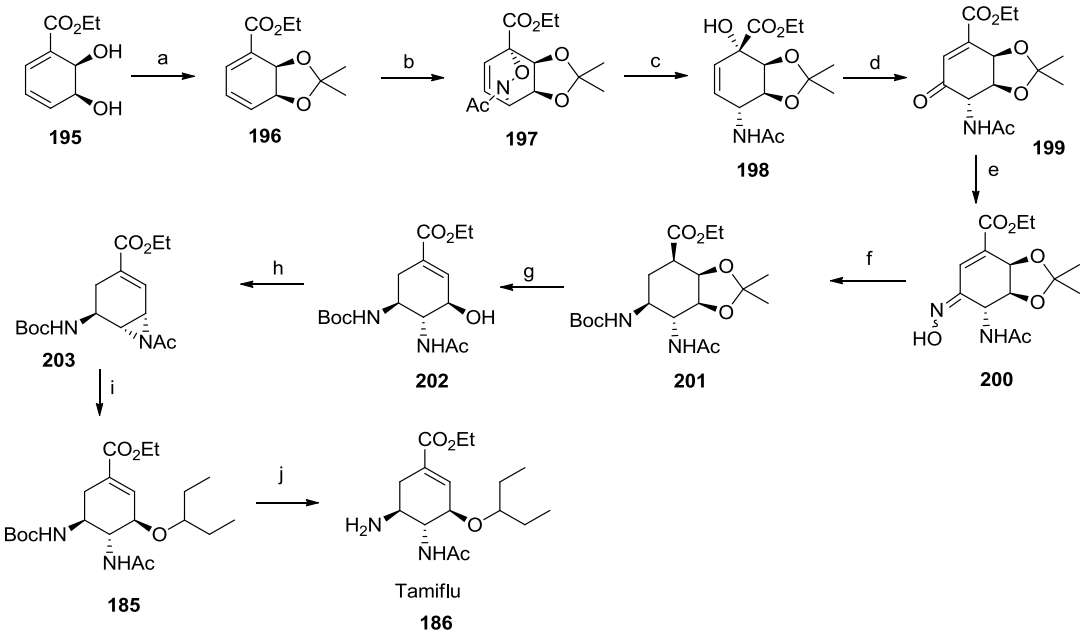


Scheme 37: Banwell's Synthesis of key Tamiflu intermediate.[95,96] Reagents and Conditions: a) *p*MBDMA, (+)-camphor sulfonic acid, toluene, 0 °C, 1.5 h; b) DIBAL-H, Et_3N, toluene, -78 °C to -30 °C, 5 h, 85%; c) i) CDI, MeCN, 0 °C, 1 h; ii) $NH_2OH{\cdot}HCl$, imidazole, 0 °C to 18 °C, 16 h, 56%; d) *p*TsCl, Et_3N, Et_2O, 0 °C to 18 °C, 16 h, 79%; e) $Cu(MeCN)_4PF_6$, K_2CO_3, MeCN, 3-pentanol, 0 °C to 18 °C, 16 h, 43%; f) LiOH, 1,4-dioxane, H_2O, 100 °C, 48 h, 85%; g) AcCl, Et_3N, 0 °C to 18 °C, 1 h, 99%; h) HCl, MeOH, 35 °C, 16 h, 90%; i) Fang's synthesis. [93]

Banwell presents 16 step enantioselective synthesis of Tamiflu, again azide free and an alternative to Fang's.

The most recent synthesis by Hudlicky *et al.*[98] has seen Tamiflu produced in 10 chemical steps in a 55% overall yield from the MAO derived *cis*-dihydrodiol **195**. It is advantageous that the starting material **195** already possesses the ethyl ester side chain which instantly reduces the number of transformations needed. Nitrogen is inserted via an acylnitroso Diels-Alder cycloaddition to form key intermediate **197**,

which is reductively opened to form **198**. The new protocol avoided the use of azide and employed [3,3] oxidative rearrangement to enone **199**. This work displays the Dauben-Michno oxidative transposition applied to electron withdrawing substituents. Formation of the oxime **200** proceeded without need for purification. Basic elimination using NaOEt formed alkene product **202**. Aziridine formation followed by Copper triflate-catalysed ring opening using 3-pentanol gave Boc protected Tamiflu product **186**.



Scheme 38: Hudlicky TamiFluSynthesis Tamiflu synthesis.[98] Reagents and Conditions: a) DMP, TsOH, r.t.; b) $CH_3CONHOH$, $NaIO_4$, MeOH, r.t., 88% 2 steps; c) $Mo(CO)_6$, MeCN, H_2O, (15:1), reflux, 87%; d) CrO_3, Ac_2O, CH_2Cl_2, 4 °C, 5 min; e) $NH_2OH{\cdot}H_2O$, EtOH, Py, r.t., 75-82% 2 steps; f) 5% Rh/Al_2O_3, H_2 (60 psi), 96% $EtOH_{(aq)}$, $(Boc)_2O$ (2-3 equiv), 93%, g) 0.05 M EtONa, EtOH, 94%; h) $PhMe_2P$, DIAD, CH_2Cl_2, 4 °C, 78%; i) 3-pentanol, $Cu(OTf)_2$, 60%; j) H_3PO_4, EtOH, 50 °C, 6 h, 81%.

In summary, Hudlicky presents a shorted and concise synthesis of Tamiflu. Key intermediate **200** can be synthesised on a multi-gram scale in just five steps in 52% yield from the MAO *cis*-dihydrodiol, this suggests that this route could be industrially viable.

2.2 Project Aims

The frequent use of the *ortho, meta* arene *cis*-dihydrodiols in aminocyclitols synthesis has been shown. In contrast the *ipso*, *ortho* arene c*is*-diol has been remarkably underexploited. In a single report, originating from the Lewis group in 2011,[76] starting with the MAO product, zwitterionic aminocyclitols, **204**, were synthesised and tested for their inhibitory activity against a range of glycosidase enzymes. In this present work we aim to synthesise aminocyclitols with the side chain in the lower oxidation state, **205**, in hope that they will have markedly different solubilities and biological activity. Figure 8.

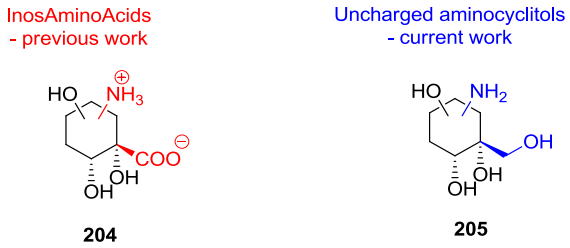
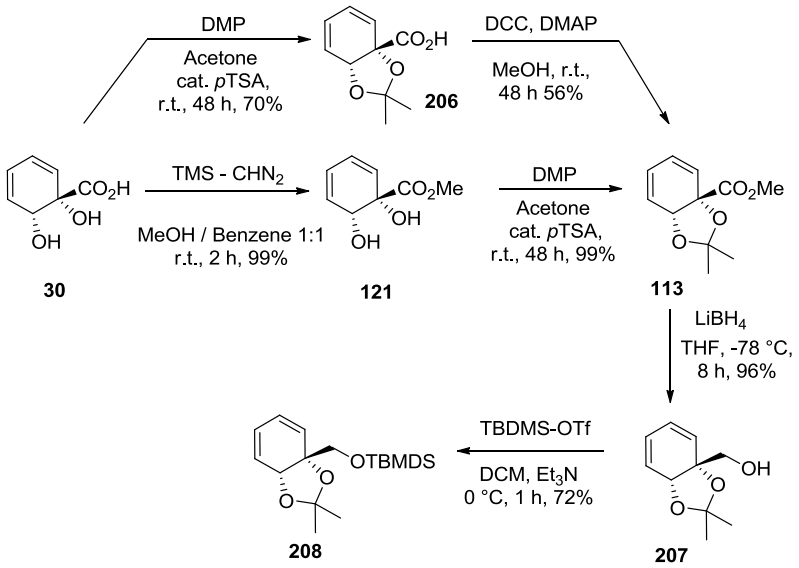


Figure 8: Current research aims.

2.3 Results and Discussion

Starting with the *ipso, otho* arene cis diol **30**, formation of acetonide-protected methyl ester **113**, could be achieved via two routes: Either following the previously utilised TMS-diazomethane procedure **121**[64] or avoiding this expense via the use of coupling agents **206**.[18] Reduction to form the corresponding alcohol **207**, was best achieved using mild $LiBH_4$. Silyl ether protection of the primary alcohol to form **208**, was needed so it is not oxidised in subsequent steps. Scheme 39.



Scheme 39: Protection of microbial arene oxidation product.

These first protections steps are necessary due to the sensitive nature of these MAO derived diene diols as they readily undergo rearomatisation under acidic **209** or basic conditions **210**.[99] Notably the *ipso, otho* arene *cis*–diols have the ability to decompose via a decarboxylation mechanism, which isn't possible for the more common *ortho, meta cis*–diols. Figure 9.

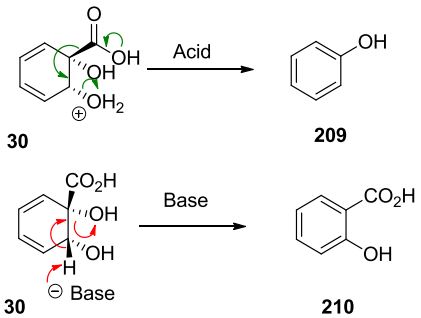
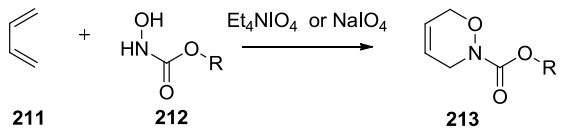


Figure 9: Rearomatisation of diene diols.

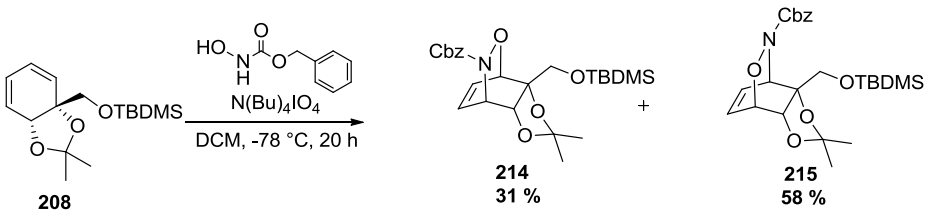
In order to form a final product in which there is controlled and predicatble stereo chemistry of all ring bound atoms, we considered the acylnitroso hetero Diels–Alder methodology. It is well known that oxidation of *N*-hydroxycarbamate esters **212** with tetraethylammonium or sodium periodate allows formation of an acyl intermediate *in situ* which is trapped by a diene **211**, to give *N*-alkoxycarbonyl-3,6-dihydro-2H-l, 2-oxazines **213**. Scheme 40. [100]



Scheme 40: Nitroso–Diels–Alder reaction

This method has been commonly applied in synthesis using the more common analogue from microbial arene oxidation **28**, both in the synthesis of aminocyclitols[87,101] and of (+)-lycoricidine [102] and has shown both high levels of stereo– and regio– specificity in good yields.

For this work, experiments were carried out in accordance with literature precedent. Scheme 41.[76]



Scheme 41: HDA reaction

The reaction proceeded in good yields, with high levels of specificity with sole attack of the dienophile to the upper face with a preference of regio– selectivity with the carbamate and silyl ether groups on the same side, which is perhaps surprising on steric grounds.

Facial selectivity studied previously[103-105] and facial selectivity observed here is consistent with that previously reported.[18,87] For both of the products isolated a clear NOESY correlation was observed between the protons of the acetonide concave methyl groups and those of the alkene. This confirmed the approach of the dieneophile to the upper face of **208** in both cases. Figure 10 & Figure 11.

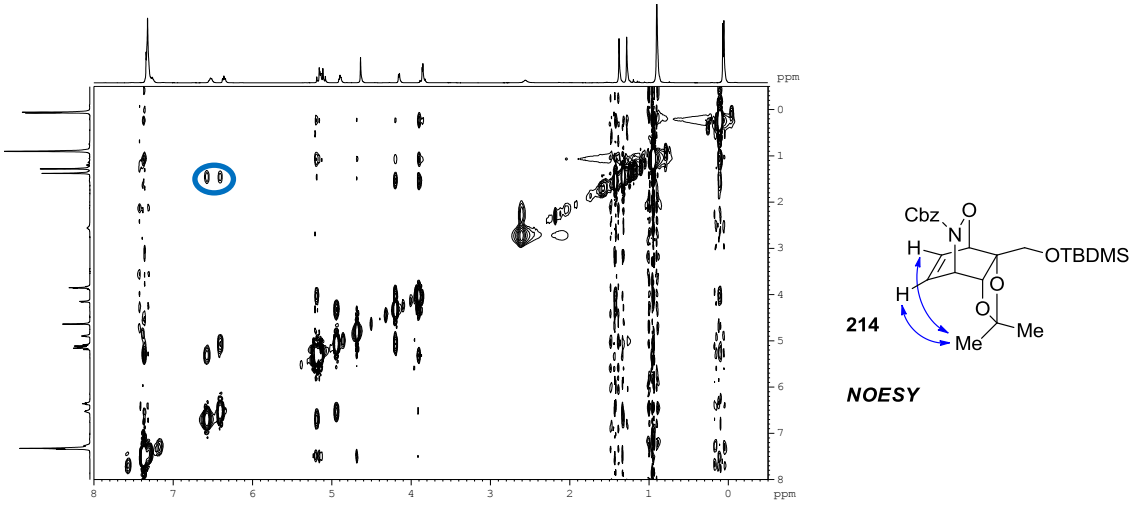


Figure 10: NOESY 2D-NMR of 214. Indicating acetonide alkene through space interaction

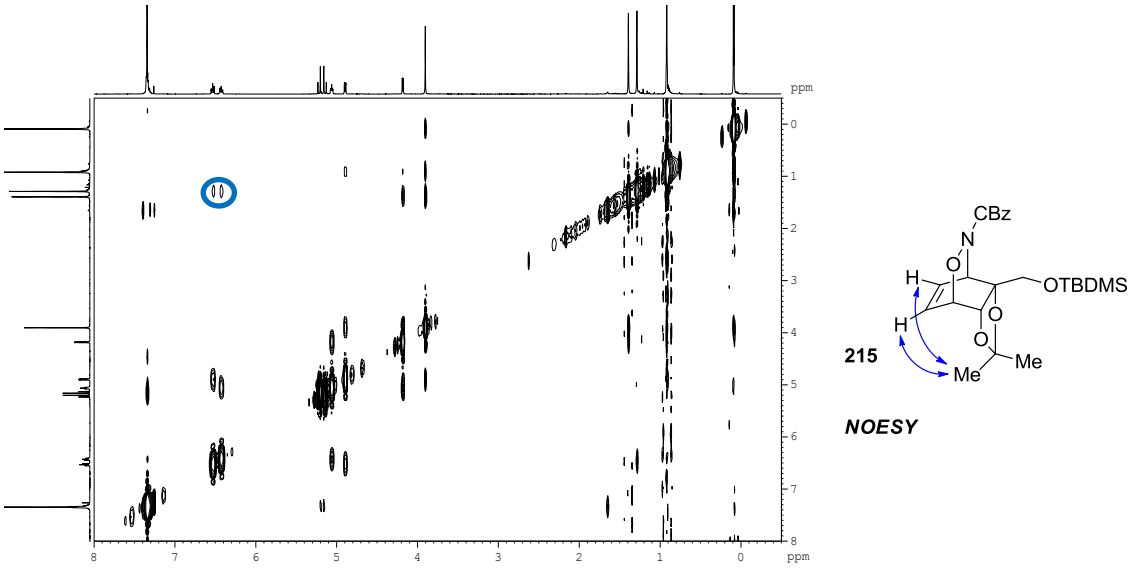


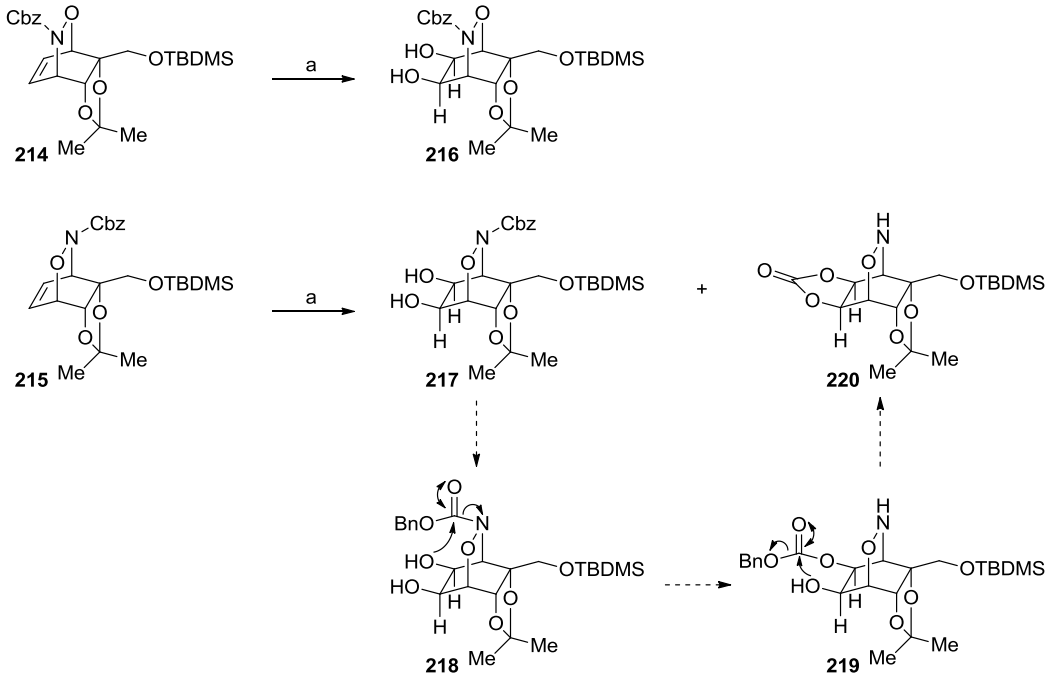
Figure 11 NOESY 2D-NMR of 215. Indicating acetonide alkene through space interaction

Identifying whether the Cbz group was distal **214** or proximal **215** to the CH_2OTBDMS side chain could not be achieved unambiguously by means of NOESY spectra alone. The assignments were instead inferred from the structure of a derivative synthesised subsequently (Figure 12) whose identity was established beyond doubt by X-ray crystallography.

2.3.1 Dihydroxylations

At this stage dihydroxylation was chosen for controlled facial selectivity for the introduction of the final oxygen functionality. Experiments were carried out in accordance with literature procedure.[76] In the case of the minor distal regio isomer **214**, a single product **216** was observed in a high yield. In contrast the major proximal regio isomer **215**, gave the desired product **217** in a moderate yield as well as a side product **220**.

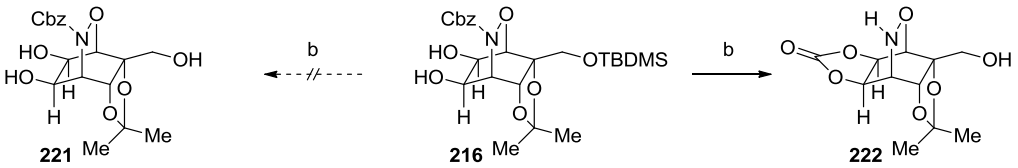
The proposed structure of the byproduct would have arisen due to reaction between the nucleophilic hydroxyl oxygen and the nearby carbamate group, thus eliminating benzyl alcohol. Scheme 42. The structure was assigned to key analytical data, through analysis of molecular mass, a characteristic $\nu_{(C=O)}$ absorbance at 1808 cm^{-1} and a ^{13}C NMR resonance at δ = 154.4 ppm.



Scheme 42: **Dihydroxylation results.** Reagents and conditions: a) OsO_4 (2 mol%), 1equiv NMO, acetone/H_2O, 4:1, r.t., 48 h, 81% **216**, 44% **217**, 17% **220**.

Additionally in support of the assigned structure **220**, in an attempt to desilylate **216** to complete the synthesis, treatment of *cis* diol **216** with TBAF did not give the expected alcohol **221**, but instead gave cyclic carbonate **222** in a 24% yield with no recovery of starting material. Scheme 43. Comparison of analytical data to **220**

indicated a Cyclic carbonate has $\nu_{(C=O)}$ = 1800 cm^{-1} and a ^{13}C NMR resonance at δ = 154.6 ppm. Furthermore the structure of **222** was secured by X-ray crystallographic analysis. Figure 12.



Scheme 43: Desilylation. Reagents and conditions: b) TBAF, THF, 0 °C, 12 h, 24%.

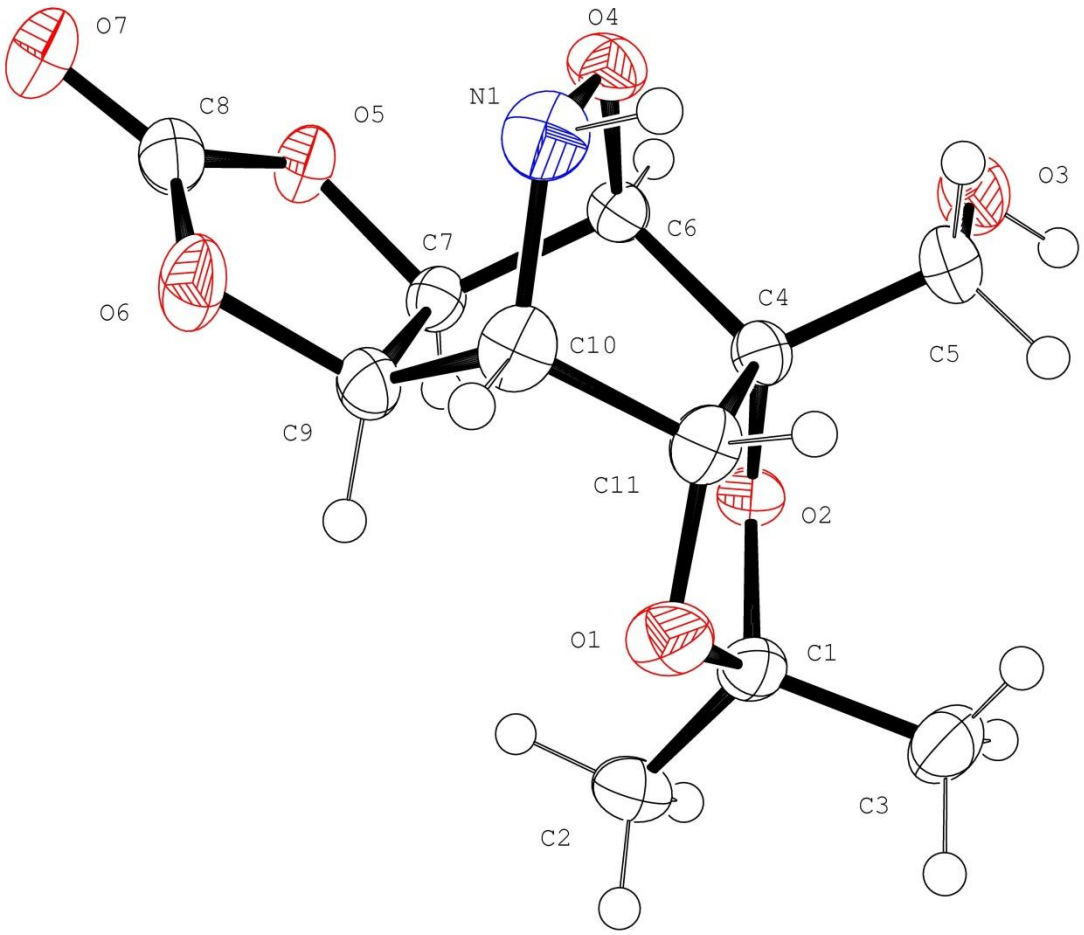
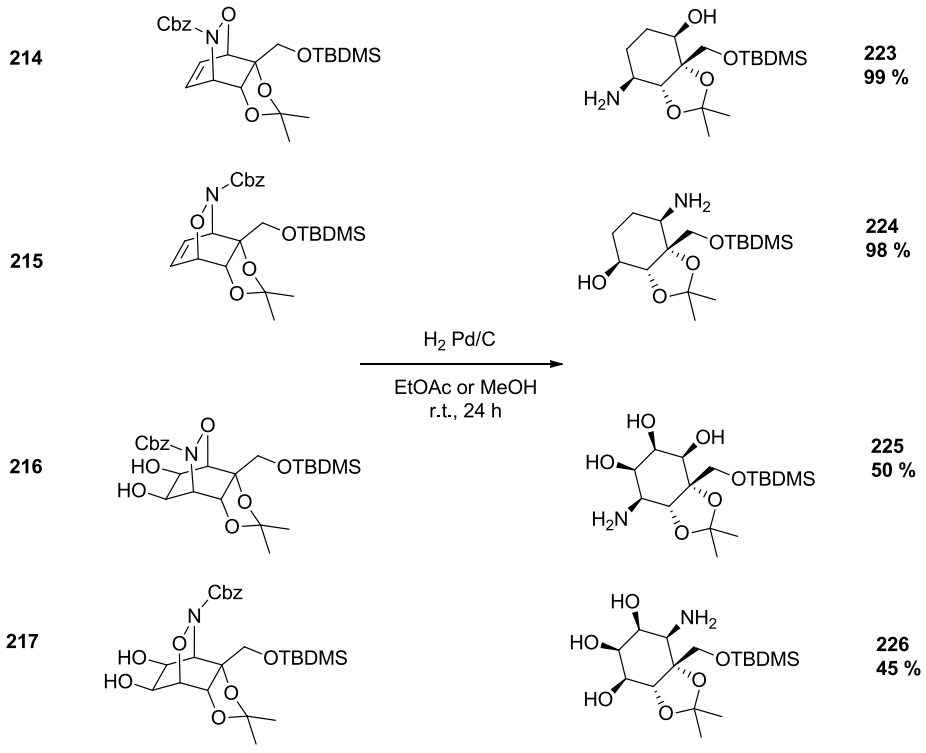


Figure 12: ORTEP diagram of X showing ellipsoids at 50% probability. H atoms are shown as spheres of arbitrary radius.

2.3.2 Hydrogenations

As silicon deprotection was not viable at this stage due to risk of forming cyclic byproducts, an alternative strategy was implemented to perform the reductive hydrogenation to open the bridging N-O bond. Hydrogenation has been shown to be a common method of opening the N-O bridge of analogous compounds.[76] Additionally under standard hydrogenation conditions we hope to perform multiple reductive transformations; deprotection of the Cbz group and reduction of the alkene.

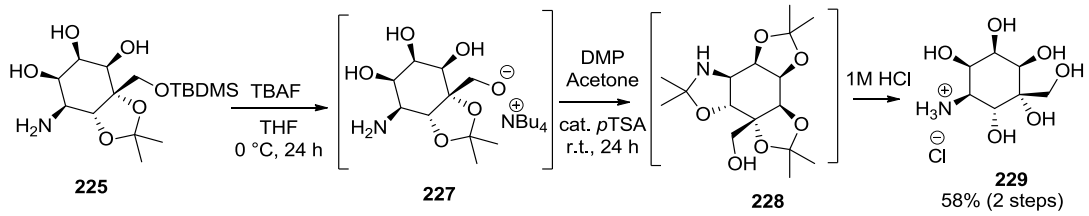
Hydrogenations on both the alkenic and dihydroxylated Diels-Alder products, **214 – 217** were subjected to hydrogenation to yield the resulting ring opened products cleanly and in good to excellent yields **223 – 226**. Scheme 44. Isolated yields of the oxygenated species **225 – 226** were significantly lower; this can be attributed to their retention on celite through purification.



Scheme 44: Hydrogenation results

2.3.3 De-protection of the silicon

With the ring opened products **223 – 226** in hand, removal of the silyl protection group to yield the corresponding alcohol was achieved with some difficulty. Scheme 45. Under standard TBAF silicon deprotection conditions the water soluble alcohol **227** was isolated contaminated with tetrabutylammonium salts. In order to remove the contaminant, **227** was subjected to acetonide formation to yield **228** which could be purified.



Scheme 45: De-protection of the silyl-alcohol.

The structure of poly-acetated **228** was tentatively inferred based on interpretation of ^{13}C NMR spectra. Three quaternary acetal carbons were observed δ_C 110.5, 109.5 and 90.2 ppm which can be used to indicate ring size and hetero atom binding. According to literature studies[106] and comparison to previously synthesised compounds, values of 110.5 & 109.5 are consistent with 5 membered rings bound through oxygen. The lower value of 90.2 ppm is indicative of an acetonide bound through nitrogen; this is in agreement of literature values of similar compounds where the quaternary carbon appears upfield, ranging from 90-95 ppm.[107,108] The NMR signals do not suggest a six membered ring, for which one would expect to observe at 97-101 ppm. [106,108]

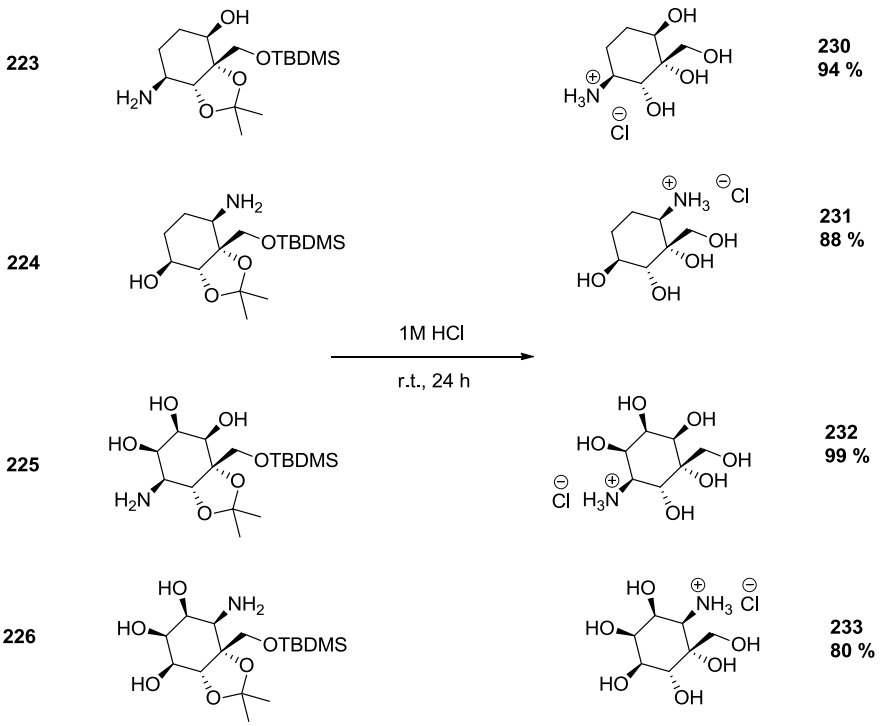
The acetonide protecting groups were then cleaved with 1M HCl to give **229** in a moderate yield of 58% over 2 steps. Although successfully obtaining the first aminocyclitol, these results suggest that TBAF is an unsuitable desilylation reagent, due to the potential contamination and extra required steps, for use with these compounds.

Additionally final aminocylitol salt **229** isolated via this route did not match the NMR spectra of the corresponding final compound **232** isolated further on within this

chapter. This suggests that possible epimerisation or rearrangement may have occurred via this route and again supports the unsuitability of this synthesis. A shorted and simpler route needs to be considered.

2.3.4 Acid deprotection – final step

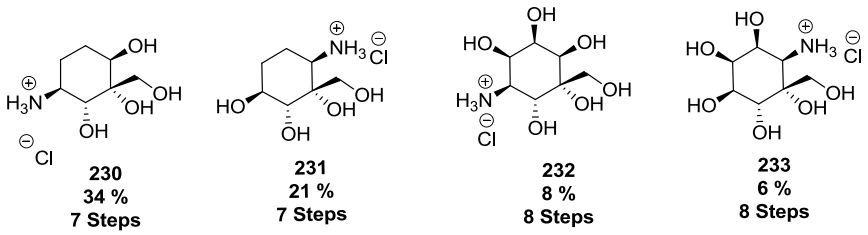
To our advantage it was found that simple treatment of **223 – 226** with 1M aqueous HCl followed by an organic wash to remove the silanol by product, resulted in cleavage of both the acetonide and silicon protecting groups cleanly and in high yields to give desired final products **230 – 233**. This was repeated in high yields for all corresponding compounds. Scheme 46.



Scheme 46: Final Products.

2.3.5 Biological assays

This work has led to the successful synthesis of four compounds of aminocyclitol structure which were tested for glycosidase inhibitory activity. [109]



Scheme 47: Final compounds for testing

Compounds synthesised were tested against α-glucosidase (type I from *S. cerevisiae*), β-glucosidase (almond), β-galactosidases (from *A. oryzae* and *E. coli*) and β-glucuronidases (from bovine liver, *E. coli* and *P. vulgata*); no inhibitory activity was observed at 100 µM. The yellow colour indicates all enzymes remained active and could still cleave the glycosidic bond to release the yellow *para*-nitro phenol from the sugar substrates.

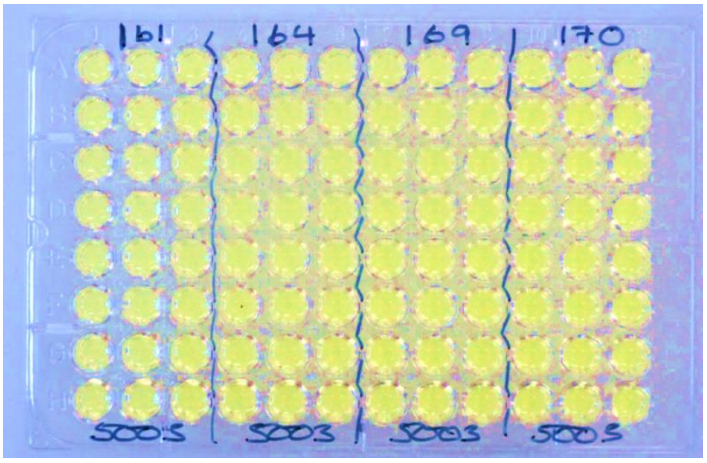


Figure 13: Biological assay results.

2.4 Conclusion: Aminocyclitols

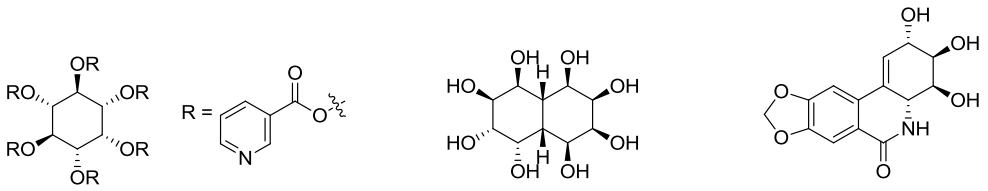
Although the compounds synthesised and tested were inactive as glycosidase inhibitors, herein we have showcased novel methodology starting with the microbial arene oxidation product through to polyhydroxylated aminated structures with up to six contiguous stereo-centres; all inserted under substrate control. Key steps include the hetero–Diels–Alder reaction and the advantageous two deprotection steps each performing multiple reactions in one pot.

3 Chapter 3: Cyclitols

Singlet oxygen formation of endoperoxides en route to novel cyclitols architectures.

3.1 Introduction

Cyclitols are polyhydroxylated alkanes, which are predominantly synthesised and studied due to their potential biological activity. Examples of biologically active compounds which contain the cyclitol motif include; Inositol hexanicotinate **234**, a commercial food supplement which releases niacin (vitamin B_3). It breaks down to form *myo*-inositol, the most common naturally occurring inositol, which is known to play an important role in cell signalling. Bicylitol **235** displayed strong inhibitory activity of α-glucosidase in yeast,{Mehta, 2005 #262} and Narciclasine **90** is a potent antineoplastic agent.{Kornienko, 2008 #263} Figure 14.



Inositol hexanicotinate **234** **235** narciclasine **90**

Figure 14: Examples of compounds which display the cyclitol motif.

Synthesis of cyclitols traditionally relies on the availability naturally occurring inositols and carbohydrate material as a source of chirality. As a result, synthetic procedures often entail many protection, deprotection and auxiliary agents, and hence tend to be wasteful and inefficient.{Duchek, 2011 #200}

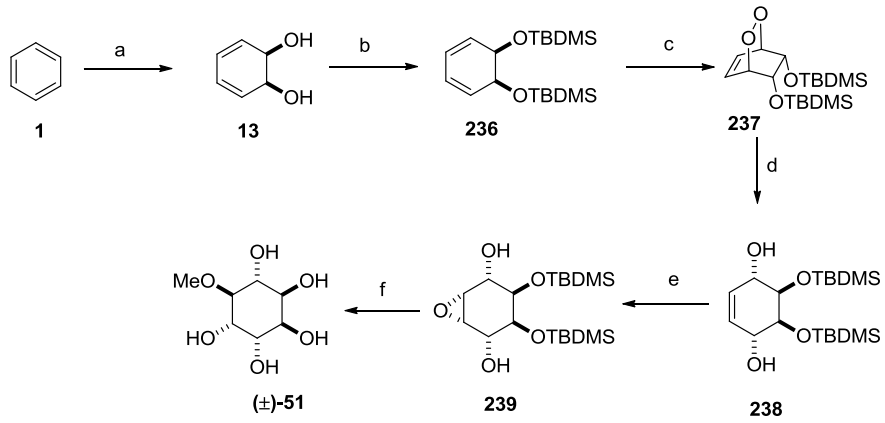
Cyclitol synthesis derived from the products of MAO offers a viable and efficient alternative. With chirality already embedded within the reactive and readily adaptable starting material, subsequent synthetic steps often proceed under substrate control though to enantiopure targets.

3.1.1 Cyclitols – Specific MAO singlet oxygen examples

Synthesis of cyclitols from *ortho, meta* diene diol products of MAO has been extensively investigated and reviewed.{Hudlicky, 1996 #265;Duchek, 2011 #200} (references therein & see introduction chapter). Here we highlight cyclitol examples

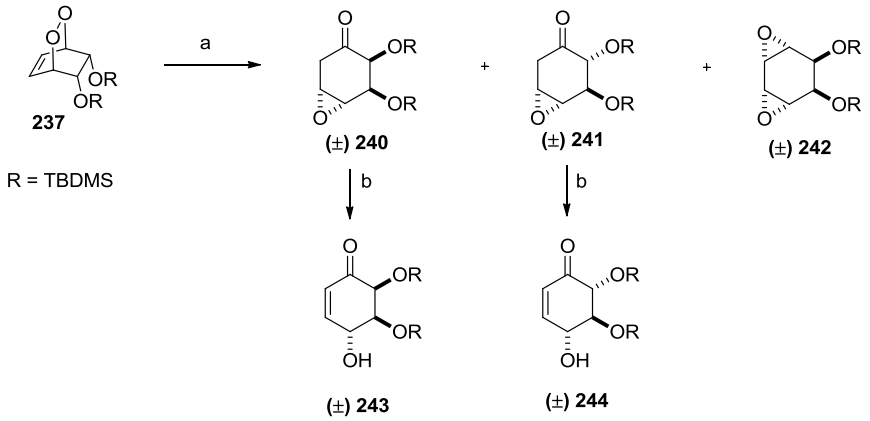
with particular emphasis on the use of singlet oxygen methodology, focusing on the formation of bridged bicyclic complexes, and the procedures utilised to open such bridged systems are discussed below.

Photochemistry has been used to access cyclitols by Carless *et al*.{Carless, 1989 #266;Carless, 1993 #201;Carless, 1992 #215} Procedures utilised singlet oxygen cycloaddition to form the endoperoxide bridge in MAO compounds **237**, followed by opening with thiourea to form alcohol **238**. Further transformation, epoxidation and ring opening led to pinitol **(±)-51** in 18% yield over 4 steps from the silylated diene **236**. Scheme 48.



Scheme 48: Carless {Carless, 1989 #266} route to pinitol 51. Reagents and conditions: a) *P. putida;* b) TBDMSCl, Et_3N, CH_2Cl_2; c) O_2, -80 °C, 32% over 3 steps; d) thiourea/MeOH; e) *m*CPBA, 95% 2 steps; f) $CF_3CO_2H_{(aq)}$, MeOH, 60%.

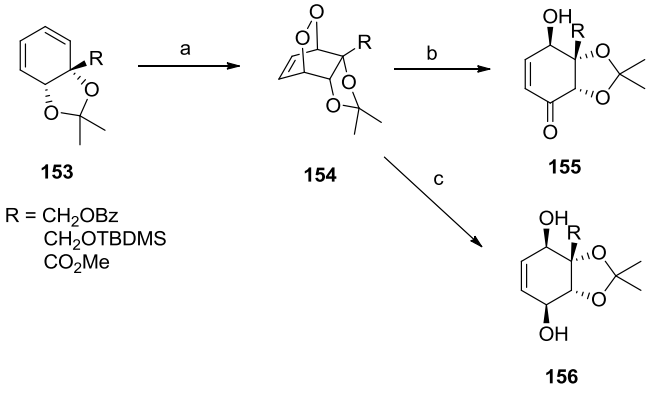
In addition Carless investigated further irradiation of endoperoxide **237** to form a mixture of β-epoxyketones **240** and **241** and bisepoxide **242**. Catalytic amounts of triethylamine led to formation of hydroxyenones **243** and **244**. Scheme 49.



Scheme 49: Carless{Carless, 1989 #266} endoperoxide bridge opening. Reagents and conditions: a) *hv*, C_6H_6, 3:1:1 of **240**:**241**:**242***;* b) cat. Et_3N, C_6H_6, 100%.

In summary, Carless identified a range of methodologies for exploiting the endoperoxides derived from MAO through to novel architectures as potential building blocks in cyclitol chemistry.

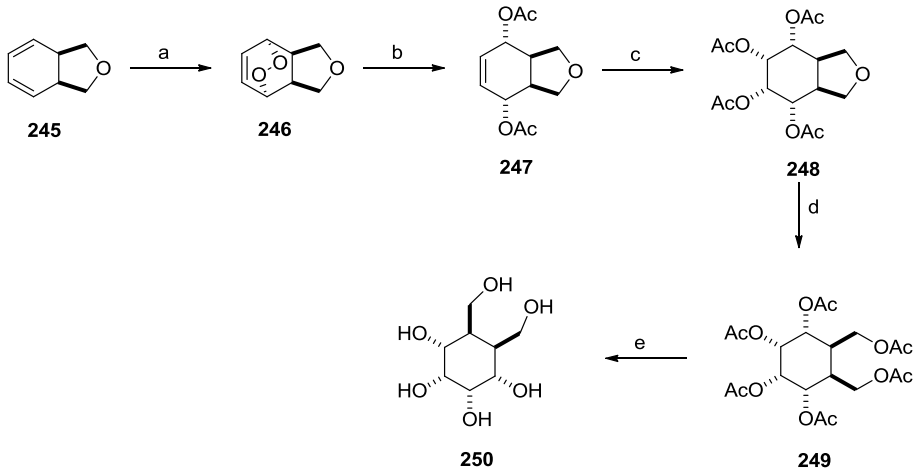
Exploiting application of the less common *ipso, otho* MAO product from benzoic acid, Lewis *et al*.{Palframan, 2012 #224} in 2012 synthesised zeylenols and zeylenones using singlet oxygen methodology to obtain bicyclic endoperoxide species **154**. Reductive opening using thiourea gave diols **156**, whereas redox neutral Kornblum–DeLaMare fragmentation accessed ketone motif **155**. Scheme 50.



Scheme 50: Synthesis of zeylenols via photooxygenation.{Palframan, 2012 #224} Reagents and conditions: a) O_2, TPP, CCl_4, 12 h, 10°C, 81-90%; b) $^{i}Pr_2NEt$, CH_2Cl_2, 94-100%; c) thiourea, CH_2Cl_2/MeOH, r.t., 12 h, 63-99%.

3.1.2 Cyclitols – specific singlet oxygen examples

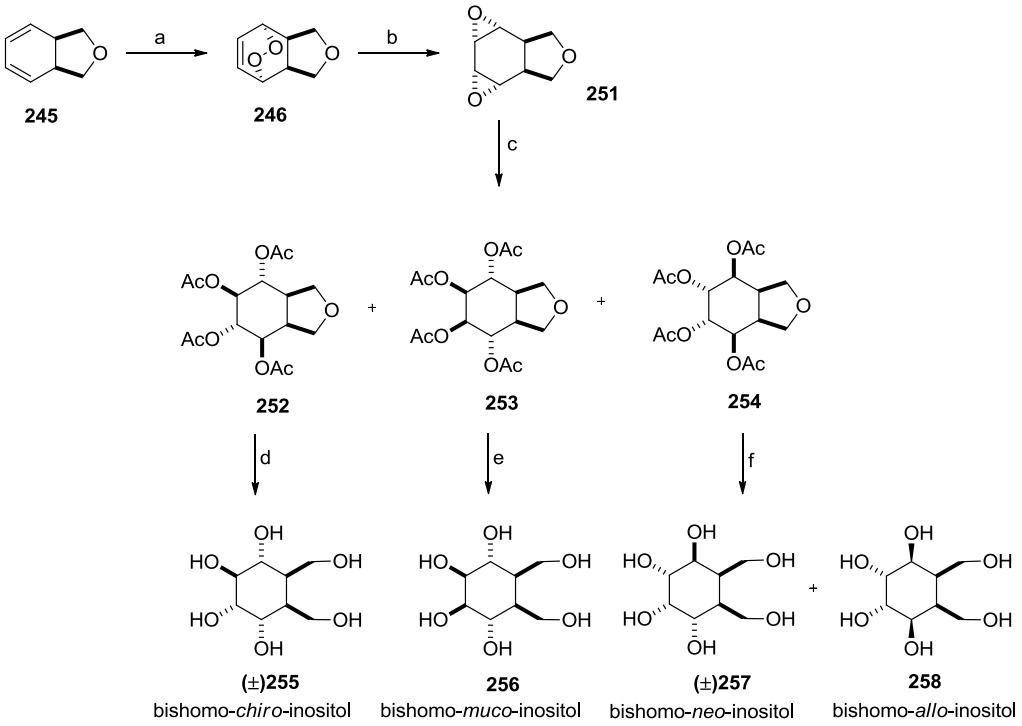
With cyclitol targets in mind, significant contribution to cyclitol synthesis employing singlet oxygen should be considered. The work of Balci *et al*.{Sutbeyaz, 1988 #251;Balci, 1985 #250;Balci, 1983 #249;Balci, 1983 #248;Balci, 1981 #247;Balci, 1981 #247;Balci, 1983 #248;Balci, 1983 #249;Balci, 1985 #250;Sutbeyaz, 1988 #251;Seçen, 1994 #55;Baran, 2008 #264;Cantekin, 2009 #62;Kilbas, 2011 #184;Baran, 2012 #246} over the last 20 years has developed methodology and synthesis based upon endoperoxide opening and cyclitol targets. In 2008 Balci{Baran, 2008 #264} synthesised various analogues of naturally occurring cyclitols, including novel architectures such as **250** which have been evaluated as glycosidase inhibitors. Scheme 51.



Scheme 51: Bacli {Baran, 2008 #264} 2008, Bishomo-inositols as glycosidase inhibitors. Reagents and conditions: a) $^1O_2$, TPP, CH_2Cl_2, *hv,* 12 h, 85%; b) thiourea, MeOH, 3 h then Py, Ac_2O, 12 h, 87%; c) OsO_4, NMO, Acetone/H_2O, then Ac_2O, Py 25 h, 73%; d) NH_2SO_3H, Ac_2O/AcOH reflux 24 h, 84%; e) NH_3, MeOH, 5 h, 91%.

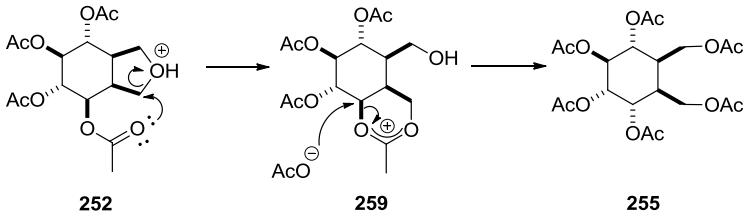
Endoperoxide **246**, derived from diene **245**, was opened using mild reduction conditions with thiourea. Dihydroxylation conditions followed by acetylation gave the tetra acetate **248**. Ring opening with sulfamic acid produced the hexa acetate **249**, which was finally subjected to deacetylation with ammonia in methanol to give the desired Bishomo-Inositol **250**. **250** was tested for its potential glycosidase inhibitory, with an inhibition rate of 57 ± 0.96% for 10 µM concentration of compound **250** which transposes to a calculated IC_{50} value of 8 µM.

Subsequent work from Balci {Baran, 2012 #246} further exploited singlet oxygen derived alkene **246**, using alternative endoperoxide opening methodology to form other novel bishomo inositol derivatives **255** – **258**. Scheme 52.



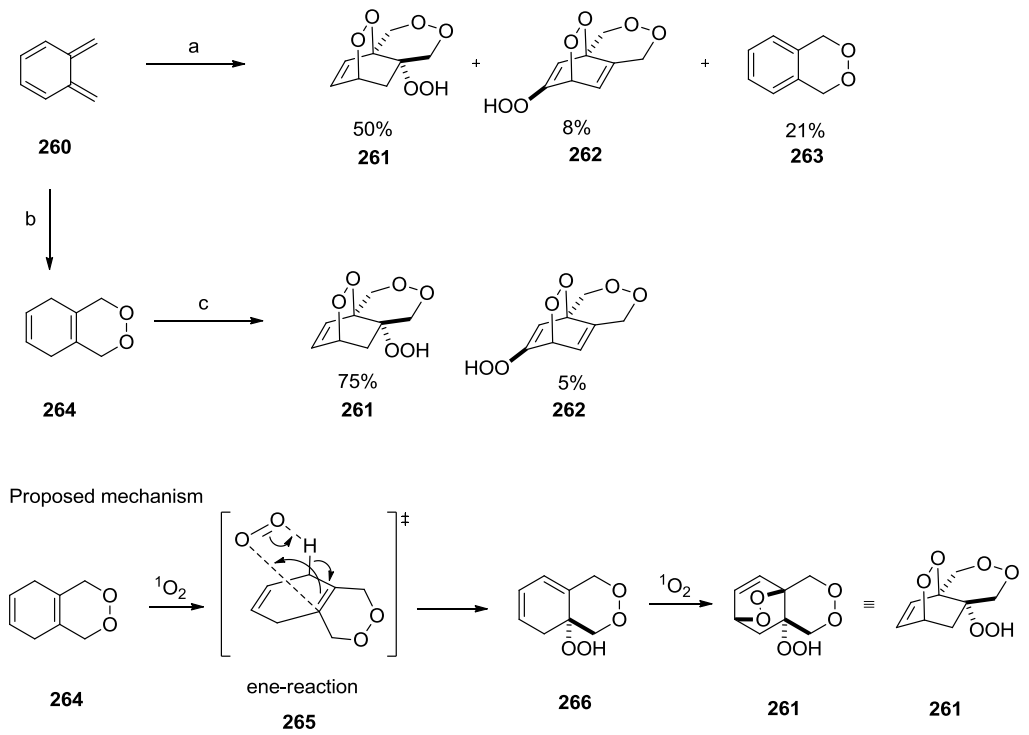
Scheme 52: Balci{Baran, 2012 #246} 2012, Bishomo-inositols as analogues. Reagents and conditions: a) $^1O_2$, TPP, CH_2Cl_2, *hv,* 12 h, 85%; b) CoTPP, CH_2Cl_2, 0 °C, 2 h, 84%; c) H_2SO_4, H_2O, 24 h, then Py, Ac_2O, 24 h, **252** 15%, **253** 50%, **254** 19%; d) i) NH_2SO_3H, Ac_2O/AcOH reflux 24 h, 70%; ii) NH_3, MeOH, 5 h, 96%. e) i) NH_2SO_3H, Ac_2O/AcOH reflux 24 h, 74%; ii) NH_3, MeOH, 5 h, 92%; f) i) NH_2SO_3H, Ac_2O/AcOH reflux 24 h; ii) NH_3, MeOH, 5 h, **257** 97%, **258** 90%;

In this work Balci exploited his known methodology {Balci, 1985 #250;Balci, 1983 #248;Balci, 1983 #249} of opening unsaturated endoperoxides with cobalt(II) tetraphenylporphyrin (CoTPP) to form the corresponding diepoxides with *syn* configuration. This work then followed similar procedures to his 2008 work with acidic ring opening followed directly by acetylation. Surprisingly tetra-acetate compounds **252** – **254** were separable via column chromatography, and fully identified and characterised based on their NMR spectroscopic data. Interestingly, formation of bishomo–*chiro*–inositol was explained via neighbouring group participation of the acetate group which lead to inversion of one of the stereocentres. It is also interesting to consider that this neighbouring group participation was not observed for the other structures. Scheme 53.



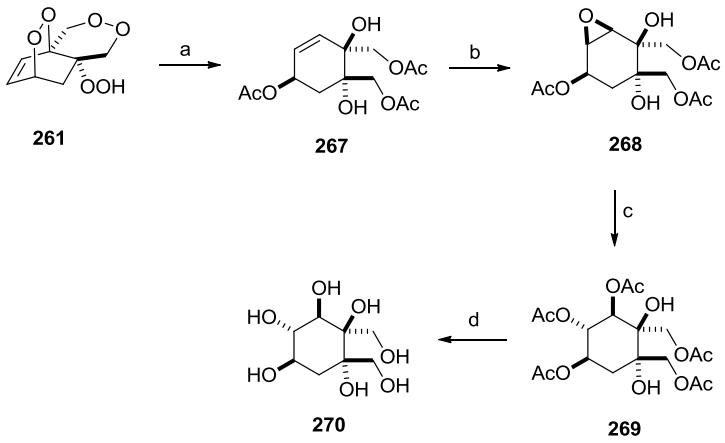
Scheme 53: Neighbouring group participation, explanation of inversion of stereochemistry.

From 2013, Balci and co-workers' most recent publication{Baran, 2013 #371} report the first example of three sequential singlet oxygen molecules being incorporated in a cascade process. Photooxygenation of diene **260** with a 500 W projection lamp, in CH_2Cl_2 at 0 °C afforded endoperoxide **264**. Further irradiation led to **264** undergoing a cascade photooxygenation reaction to form the two regioisomeric tricyclic bis-endoper-oxides **261** and **262**. The formation of the major regioisomer **261** was attributed to the second attack of singlet oxygen to the more substituted double bond in intermediate diene endoperoxide **264**, as supported with their previous findings.{Yardımcı, 2006 #372} Following the proposed mechanism, diene **264** undergoes an ene reaction to form diene **266** which then reacts for the third and final time with singlet oxygen to form final product **261**. Scheme 54.



Scheme 54: Balci 2013{Baran, 2013 #371} Trisequential Photooxygenation reaction. Reagents and conditions: a) $^1O_2$, TPP, CH_2Cl_2, *hv* ,r.t., 40 h; b) $^1O_2$, TPP, CH_2Cl_2, *hv* , 0 °C, 25 min, 86%; c) $^1O_2$, TPP, CH_2Cl_2, *hv* , 0 °C, 56 h. 500 W projection lamp used.

Exploiting the highly functionalized structure of endoperoxide **261** towards cyclitol motifs Balci followed his previous experimental precedent of thiourea endoperoxide opening, acetate protection, epoxidation, and deprotection. Balci displayed elegant synthesis of carbasugar **270** in a 60% yield over 4 steps from the endoperoxide **261**. Scheme 55.

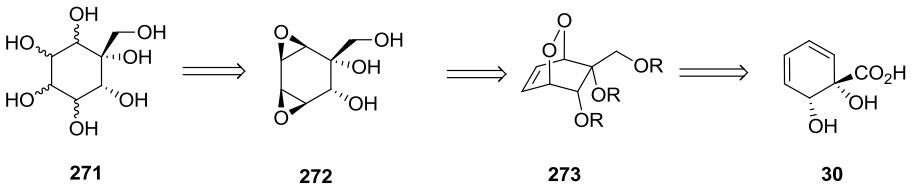


Scheme 55: Balci {Baran, 2013 #371} Carbasugar synthesis from endoperoxides. Reagents and conditions: a) i) thiourea/MeOH ii) Ac_2O, Py, 82%; b) *m*CPBA, CH_2Cl_2, 67%; c) i) H^+/H_2O ii) Ac_2O, Py, 78%; d) NH_3, MeOH, 95%.

In summary, Balci's use of singlet oxygen photochemistry has allowed access to highly oxygenated and functionalised architectures which prove ideal substrates for the synthesis of carbasugars. In many cases procedures obtain single enantiomers, which have been proven to be biologically active. Balci's simple protocols highlight the ease of handling and purification of these types of structures. These approaches could be applied to other dienes, for example those derived from MAO, en route to enatio-pure carbasugar motifs.

3.2 Aims

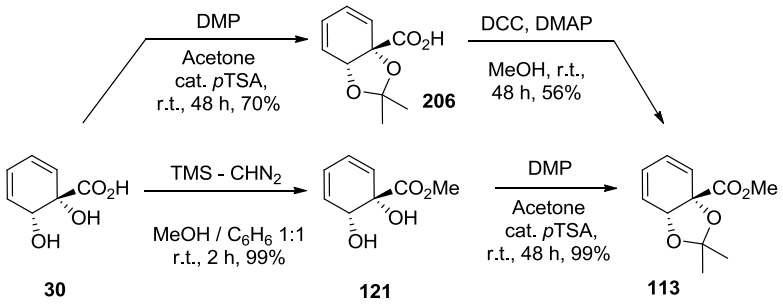
The aim of this project was to synthesise inositol analogues **271** from MAO products **30**. Utilising singlet oxygen methodology already president within the Lewis group, and methodology inspired from Balci's work discussed above. The proposed synthetic procedure is shown below. Scheme 56.



Scheme 56: Proposed route to inositol analogues from MAO product 30.

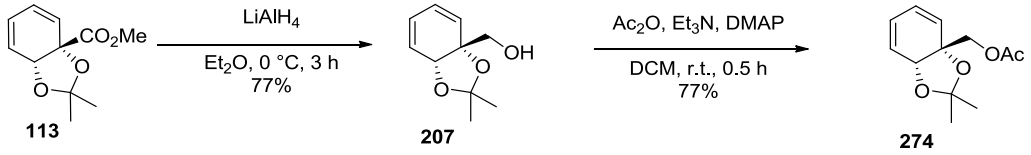
3.3 Results and Discussion

Following literature procedures through to known compounds, previously discussed methyl ester **113** was synthesised via two routes. (Chapter 1 Aminocyclitols) Scheme 57.



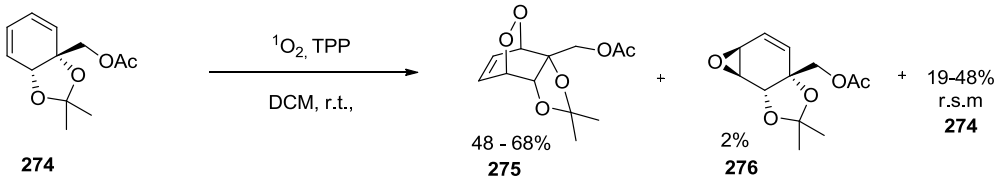
Scheme 57: Synthesis of methyl ester 113.

Formation of the reduced side chain, **207**, was achieved using $LiAlH_4$, with a reasonable yield of 77% which is enhanced from previous reports using $LiBH_4$ 68%.{Palframan, 2012 #224} Standard acetylation proceeded well to form **274**. Scheme 58.



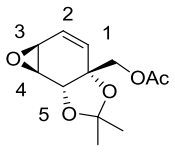
Scheme 58: Synthesis of acetylated diene 274.

Following synthetic procedures from Widdowson{Jenkins, 1995 #11} Balci{Baran, 2012 #246} and Lewis{Palframan, 2012 #224} reaction of **274** with $^1O_2$ yielded endoperoxide **275**, in varying yields from 36% to 68% recovering starting material and in one instance a byproduct **276**. Higher yields were obtained by utilising slow addition of TPP (5,10,15,20-Tetraphenyl-21H,23H-porphine) dissolved in CH_2Cl_2 and irradiating for at least 10 h. It was found that after this time reaction progression slowed. After approximately 10 h the purple pink colour of the solution would start to discolour to green/brown. This indicated that the TPP had degraded and was deactivated. Concentrated reaction solutions which contained more TPP did not precede any faster and seemed to degrade even quicker. Additionally these yields are lower than those previously reported,{Palframan, 2012 #224} however avoid the use of extremely toxic carbon tetrachloride. Scheme 59.

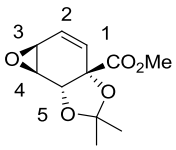


Scheme 59: $^1O_2$ yielded endoperoxide 275 and byproduct 276.

The unexpected byproduct **276** was fully characterised by interpretation of 2D-NMR spectra and mass spectrometry. Additional support for this structure comes from comparison to known literature compound **277**, which shows very similar chemical resonances and splitting pattern in ^1H NMR spectra. This also supports the proposed stereochemistry around the epoxide. Table 2. {Myers, 2001 #12}



276



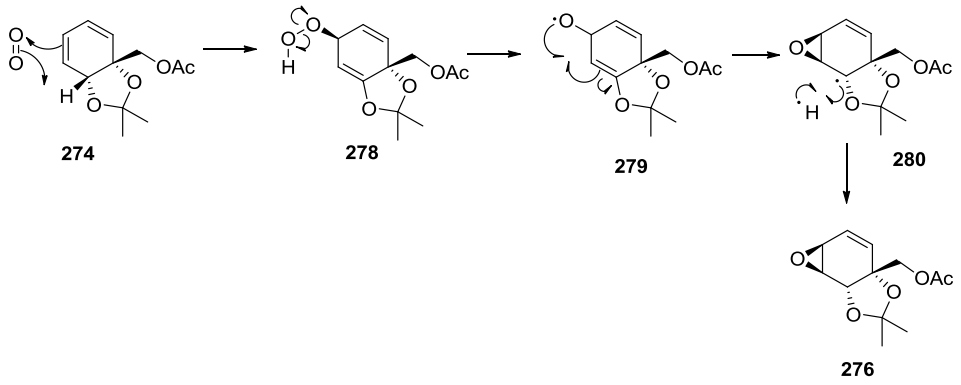
277

Scheme 60: Myers' {Myers, 2001 #12} synthesised epoxide, for comparison to byproduct 276.

	Compound 276	Myers 277 {Myers, 2001 #12}
H2	6.09 (1H, dd, *J* = 10.0, 4.0 Hz)	6.18 (1H, dd, *J* = 10.4, 4.4 Hz)
H3	5.70 (1H, dt, *J* = 10.0 1.5 Hz)	5.84 (1H, dt, *J* = 10.0, 1.2 Hz)
H5	4.65 (1H, t, *J* = 1.0 Hz)	5.17 (1H, m)
H4	3.64 (1H, dd, *J* = 3.5, 2.5 Hz)	3.65 (1H, dd, 1H, *J* = 3.6, 2.0 Hz)
H3	3.37 (1H, m)	3.39 (1H, m)

Table 2: Comparison of byproduct 276 to literature NMR spectroscopy values.

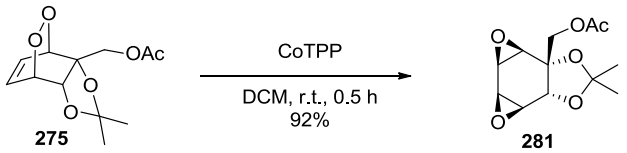
In consideration of how byproduct **276** was formed, a mechanism has been proposed below. Scheme 61. Literature suggests that singlet oxygen can react with alkenes via an ene-reaction, to form intermediate peroxide **278**. This intermediate has been previously observed by Balci in 2013,{Baran, 2013 #371} Davis 1996,{Davis, 1996 #399} and Carless in 1989.{Carless, 1989 #266} Decomposition and rearrangement through radical reactions leads to formation of the observed by product **276**. {Frimer, 1979 #400}



Scheme 61: Proposed mechanism for the formation of byproduct 276.

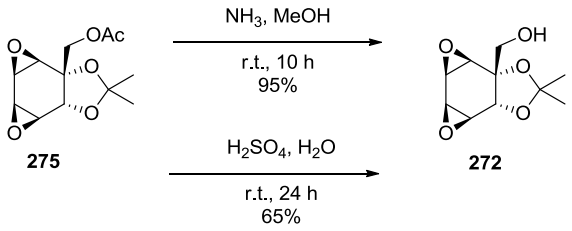
Following methodology from Balci{Baran, 2012 #246;Balci, 1983 #248;Balci, 1983 #249;Balci, 1985 #250;Sutbeyaz, 1988 #251} unsaturated bicylic endoperoxides can be converted to the diepoxide with *syn*-configuration on treatment with cobalt (II)

tetraphenylporphyrin (CoTPP). On treatment of **275** under these conditions, bisepoxide **281** was isolated in near quantitative yields. Scheme 62.



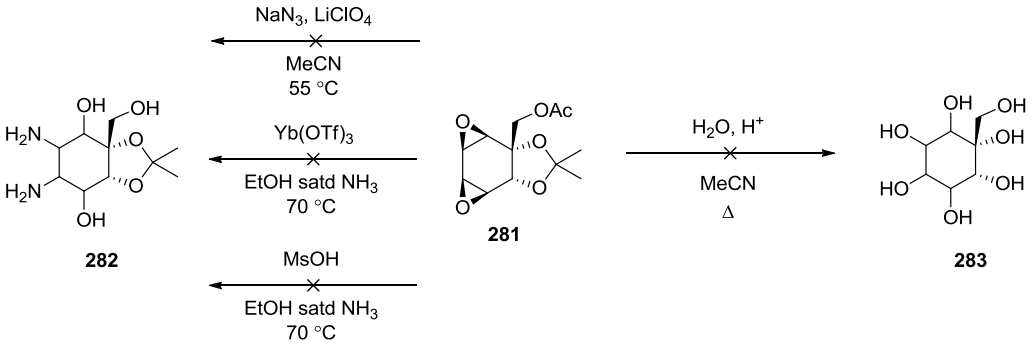
Scheme 62: Formation of endoperoxide 281.

Opening of the bisepoxide **281** was evaluated using various experimental procedures. Attempts via acid hydrolysis and ammonia in methanol were unsuccessful and both resulted only in cleavage of the acetate to form alcohol **272**. Scheme 63.



Scheme 63: Diepoxide opening resulted in acetal hydrolysis to form 272.

Attempts at nitrogen incorporation was undertaken following procedures using $Yb(OTf)_3$, MsOH,{Kaburagi, 2007 #311} NaN_3}Cristina, 1999 #253} all attempts were unsuccessful. Scheme 64.

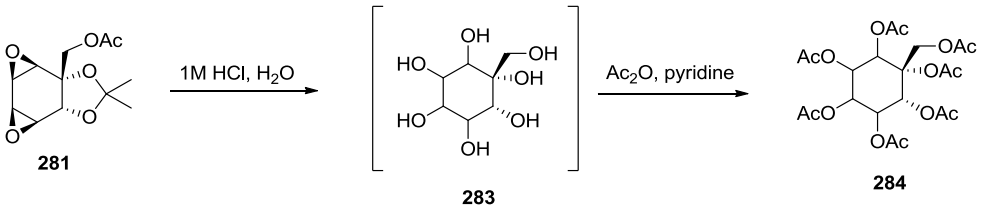


Scheme 64: Endoperoxide opening using nitrogen nucleophiles, unsuccessful.

Attempts to open the bisepoxide **281** under forcing conditions of refluxed aqueous acid to form **283** was attempted and unsuccessful. The expected poly-ol product, from aqueous acid ring opening, **283** would be extremely polar and difficult to column, purify or isolate. Considering methodology from Balci{Baran, 2012 #246}, in which acid catalysed ring opening was instantly followed by acetylation, the

expected poly acetals products should be able to be purified by column chromatography.

Following this procedure, **281** was subjected to aqueous acid to form **283** *in situ,* then subsequent acetylation to form **284**. Variations in reaction time, equivalents of all reagents and temperature were investigated. Crude reaction mixtures did indicate formation of acetylated compounds; however these proved very difficult to isolate and purify. This is potentially due to partially acetylated products all having very similar polarity and hence extremely difficult to separate due to co-elution via column chromatography. Scheme 65.



Scheme 65: Formation of polyacetals 284.

In a rare example, a single poly acetate product (later assigned as **290A)** was isolated in pure form from one of these reactions, 3mg <1% yield. Enough material was isolated only to obtain full NMR data (no further derivatisation was undertaken). Below, rationale and discussion follows to suggest which product and conformer has been isolated.

Initial inspection of the NMR spectra indicates that the compound is a tetra acetate, with four distinct CH_3 regions between 1.99 – 2.20 ppm. Additionally the acetonide protecting group has been removed as there is an absence of quaternary acetonide carbon signal in the ^{13}C spectrum and the methyl acetonide groups from the ^{1}H proton spectrum. Figure 15 & Figure 16.

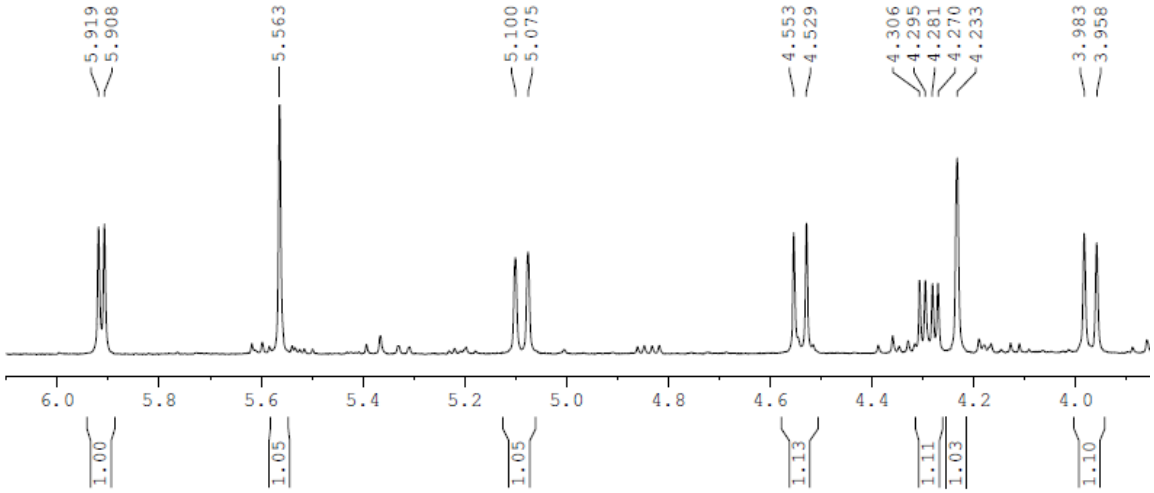


Figure 15: ^{1}H NMR spectrum of isolated polyacetate 290A. (500 MHz $CDCl_3$.)

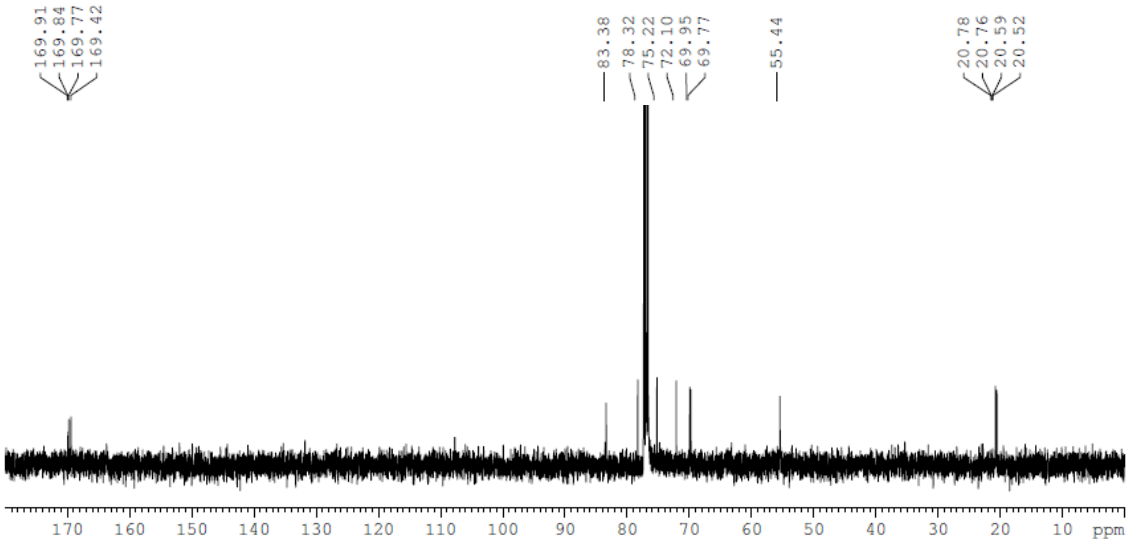
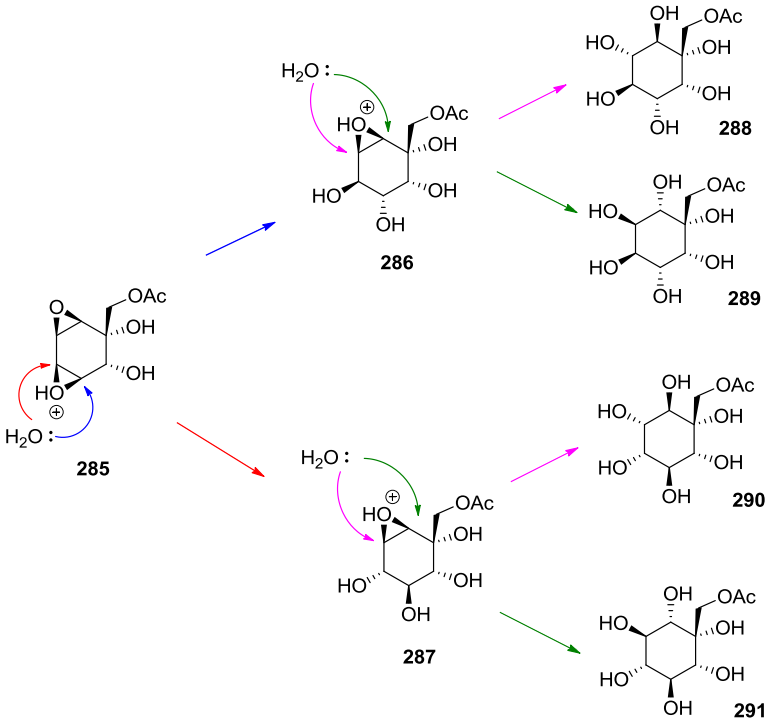


Figure 16: ^{13}C NMR spectra of isolated polyacetate 290A. (100 MHz $CDCl_3$.)

In consideration of the mechanism and possible products that could be formed from the reaction of acidic water ring opening the bisepoxide, four possible products **288** - **291** may be formed. Scheme 66.



Scheme 66: Possible products from acid water hydrolysis of bisepoxide 285

Via interpretation of the proton NMR spectra of the isolated tetra acetate, coupling constants of the ring protons suggest a $H_{ax} - H_{ax} - H_{eq} - H_? - H_?$ arrangement around the cyclohexane ring according to coupling constants. {Minch, 1994 #258;Karplus, 1963 #257} The Karplus equation gives an estimation of $^3J_{H\text{-}H}$ proton coupling constants based on their dihedral angle, and *vice versa*. The strict relationship is only applied to unstrained, saturated unsubstituted hydrocarbons, however the equation and its more complicated variants can be applied to deduce the conformation of ring systems. E.g. cyclohexane,{Garbisch, 1968 #260;Karplus, 1963 #257} monosubstituted cyclohexanes,{Jensen, 1969 #259} polyhydroxylated cyclohexanes.{McCasland, 1968 #261} In summary, larger $^3J_{H\text{-}H}$ proton coupling constants are observed between H_{ax} – H_{ax} protons (9 – 12 Hz) and values are typically less for $H_{eq} - H_{ax}$ or $H_{eq} - H_{eq}$ (3 – 4 Hz).

Analysis of NMR spectra of isolated polyacetate indicates a large coupling constant of 10 Hz, between the resonances at 5.09 ppm and 4.29 ppm, indicating a $H_{ax} - H_{ax}$ conformation. If 5.09 ppm is an axial position, within the proposed structure, this proton must be adjacent to the quaternary carbon, hence only coupling to one other proton, as we do not observe any smaller splitting due to $H_{ax} - H_{eq}$ coupling.

Proton resonance at 4.29 ppm is split into a double doublet, coupling to 5.91 ppm with a coupling constant of 4.5 Hz, indicating a $H_{ax} - H_{eq}$ interaction. All other peaks appear as singlets, suggesting the angle between H_{eq} and subsequent protons is ~90°, hence it cannot be stated with certainty whether the protons are in an axial or equatorial environment. Figure 15.

In consideration of all possible conformations (simplified to be based on cyclohexane conformations) of all possible products, a $H_{ax} - H_{ax} - H_{eq}$ relationship needs to be present, with the first H_{ax} adjacent to the quaternary carbon. Two possible conformers have been identified which display this pattern. Figure 17. (Assignments of acetate positions has been inferred later, substituents have been simplified to OR in this instance, where R = H or Ac)

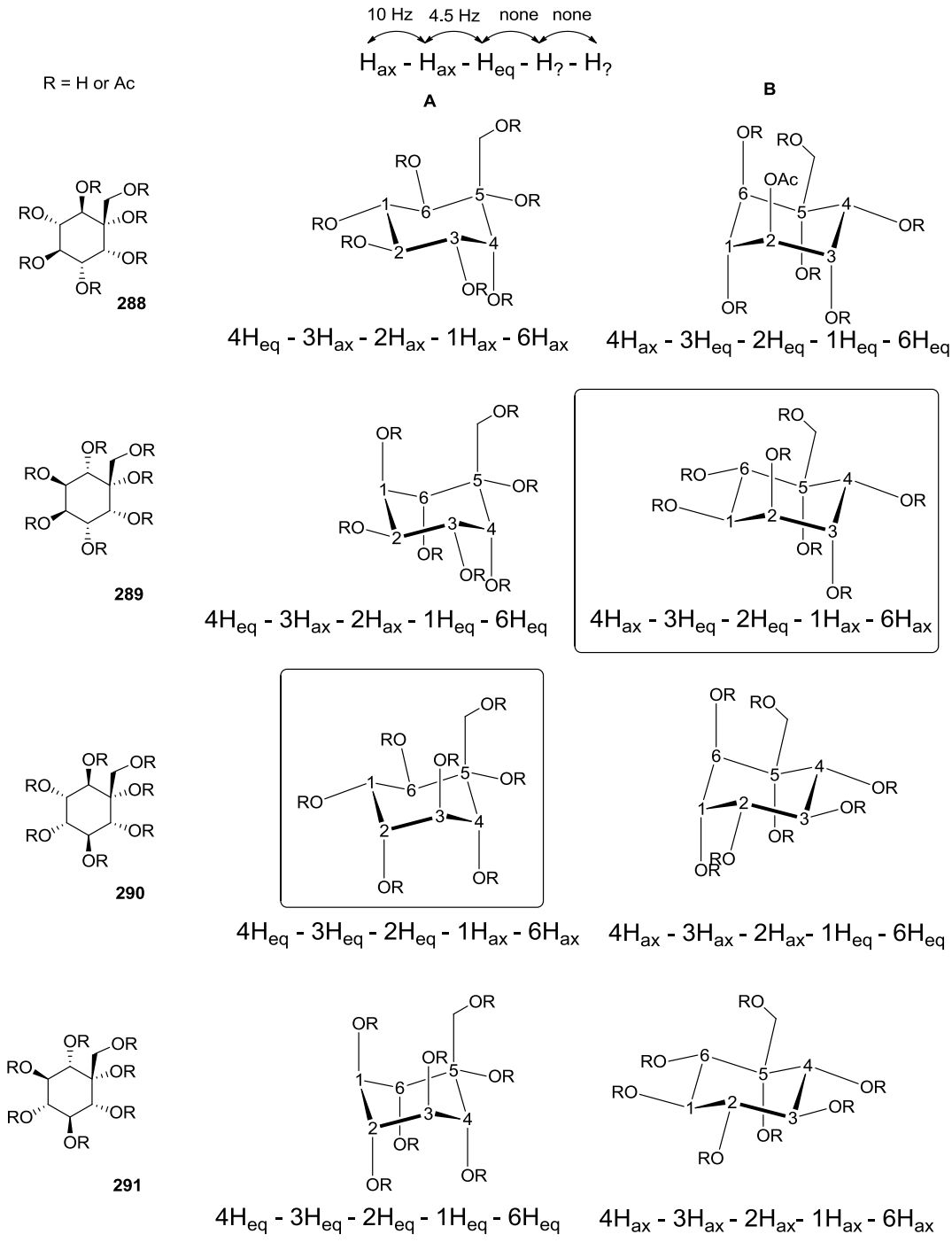


Figure 17: Possible conformations.

Conformer **289B** has been discounted as NOESY 2D NMR spectroscopy indicates through space interaction between H^1, (identified at 4.29 ppm as a doublet of doublets, displaying coupling to adjacent axial and equatorial protons) and CH_2, which is only possible in the conformation of **290A**. Figure 18.

Additionally Conformer **289B** has been discounted as from proposed conformational order, $6H_{ax} - 1H_{ax} - 2H_{eq} - 3H_{eq} - 4H_{ax}$, expected coupling between $3H_{eq} - 4H_{ax}$ with a coupling constant between 3 – 4 Hz is not observed.

This argument further supports the choice of conformer **290A**, as from proposed conformational order, $6H_{ax} - 1H_{ax} - 2H_{eq} - 3H_{eq} - 4H_{eq}$, no coupling between $3H_{eq} - 4H_{eq}$ is observed; hence $3H_{eq}$ and $4H_{eq}$ appear as singlets.

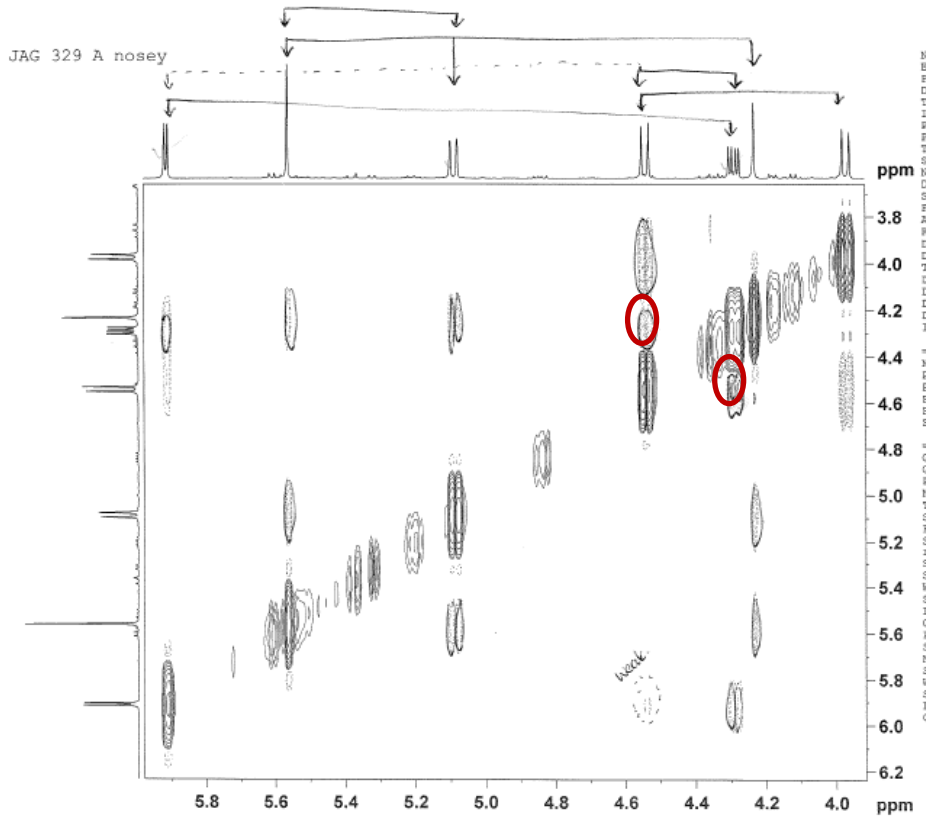


Figure 18: NOESY spectra of poly acetate, indicating through space interaction between H^1 4.29 ppm and CH_2.

Further consideration of 2D spectroscopic assignments of carbons and other protons can be made, albeit not fully due to the two ambiguous singlet resonances which cannot be assigned as they both show NOESY through space correlation to 5.08 ppm. Figure 18. Additional ambiguity arises, as regards the question of which alcohols are acetylated. It could be assumed that the most down field ^1H resonances (5.91, 5.56, 5.09 ppm and the CH_2) are acetylated. On this basis, **290A** is tentatively assigned the structure shown in Figure 19.

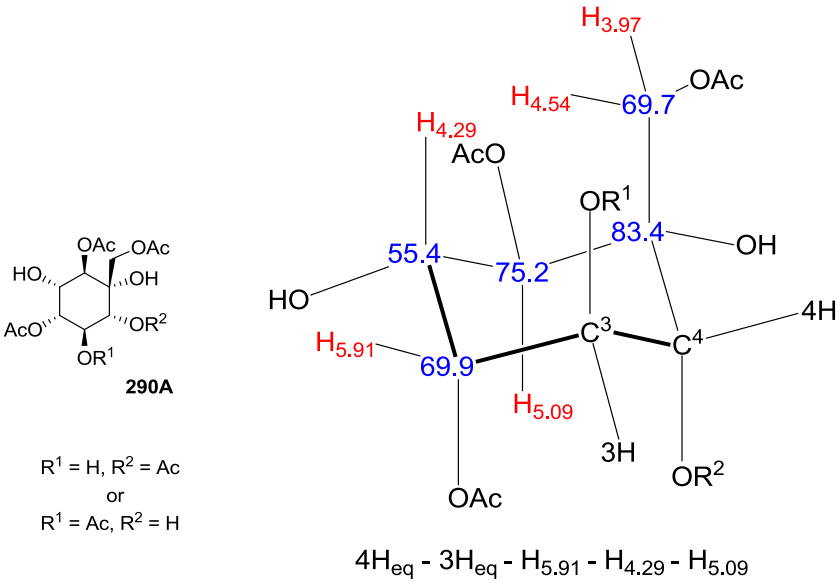


Figure 19: further assignment of NMR signals. Indicating assigned ^{13}C and ^{1}H NMR spectroscopy resonances.

3.4 Conclusion

Despite being able to fully characterise this compound, it is obvious that under these reaction conditions, multiple products form of similar polarity, and as a result are difficult to purify and separate. Additionally it is possible that neighbouring group participation could be in effect, as shown with Balci,{Baran, 2012 #246} which would further complicate mixture and lead to difficult chromographic separations.

Future work would look at selective ring opening, with the use of larger nucleophiles to induce some selectivity. At this point, no further work was carried out in this area.

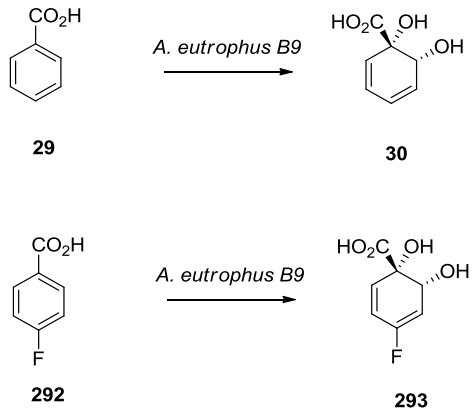
4 Chapter 4: Bromine Substrates for BZDO

4.1 Introduction: Halogenated Substrates MAO [134,135]

There are many examples within the literature of halogenated, substituted and polycyclic aromatic compounds which when subjected to MAO give *ortho, meta* substituted dienes **28**. Scheme 67. This field has been reviewed in the earlier literature introduction.

Scheme 67: Dioxygenase enzymes which metabolise substituted aromatics.

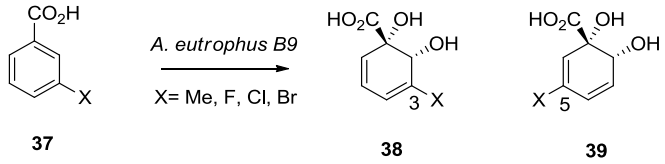
Substituted benzoate substrates that may be elaborated via BZDO mediated dihydroxylation to give *ipso, ortho* substituted dienes are comparably less exploited. From the first report of *A. eutrophus* B9, Reiner & Hageman 1971, [21] identified 3,5 – cyclohexadiene-1,2-diol-1-carboxylic acid **30** as the MAO product of benzoic acid. This preliminary study indicated that substituted benozates could be metabolised, albeit at appreciably slower rates. Scheme 68.



Scheme 68: Reiner & Hageman 1971, *A. eutrophus* B9 and substituted aromatics. [21]

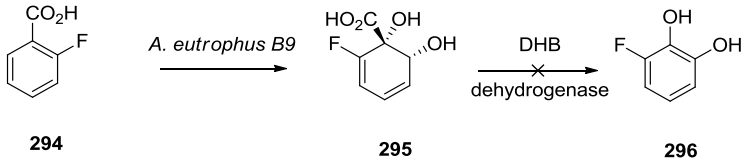
Two years later, in 1973,[26] Knackmuss and Reineke investigated mono, di-chloro and methyl- substituted benzoates, and although *A. eutrophus* B9 showed the ability to metabolise such substrates, again rates were 10-1000 times slower

depending on the specific substrate. This study was further expanded in 1978[27,28] to include bromo- and fluorobenzoates, and once again a decrease in rate was observed, which was attributed to the steric effects of the substituents. The relative rates of oxidation, according to the substituent were established to be F>Cl>Me>Br. Regarding regioselectivity, *meta* substituted benzoates were metabolised more readily than *ortho* or *para*. For *meta*-substituted substrates, a preference for formation of the 3-substitued diene product **38** over the 5-substituted isomer **39** was reported. Scheme 69.



Scheme 69: Knackmus 1978, preference for 3-substitued diene product 38 observed. [27,28]

Later Knackmuss in 1980[136] found that *A. eutrophus* B9 had the ability to use 2-fluorobenzoate **294** as a sole carbon source and produce 6-fluoro-3,5-cyclohexadiene-1,2-diol-1-carboxylic acid **295** as a single product. Knackmuss attributed this to a defective DHB-dehydrogenase enzyme, preventing formation of 3-fluoro catechol **296**. Scheme 4.



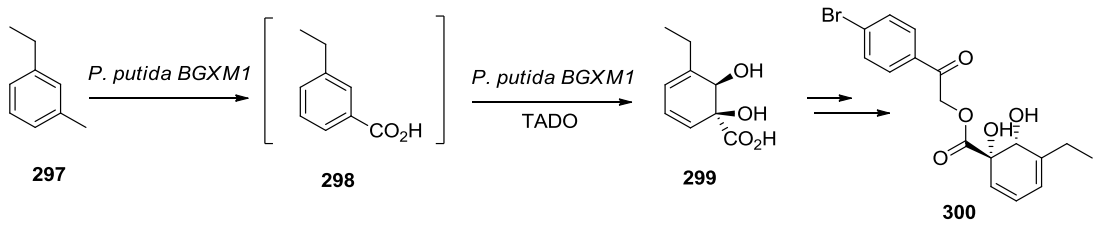
Scheme 70: Knackmuss 1980, identified that the reason for accumulation of diene 295 was due to the defective enzyme. [136]

Other organisms expressing BZDOs have been show to metabolise substituted benzoates. For example, *Pseudomonas mt-2*. [137,138] and *P. putida* JT 103[19] have been used for the biotransformation of fluorinated benzoates. BZDO has also been expressed in recombinant *E.coli*.[139-141]

As highlighted above there is a plethora of research, dating back to the 1980's, investigating whether substituted benzoates can be metabolised by dioxygenase-

expressing bacteria. With a range of homochiral products identified and dioxygenase expression in stable recombinant strains, it is surprising that there is very little use of these substituted benzoate products in further synthetic applications.

The sole literature example, displaying the synthetic use of substituted *ipso*, *ortho* *cis*-diols, was reported by Banwell *et al.* in their approach to vinblastine. Scheme 71.[142] With access to *P.putida* BGXM1, which contains enzymes capable of oxidising toluenes to benzoic acids and TADO enzymes capable of the di-hydroxylation of toluates; Banwell utilised this in an elegant one pot microbial transformation of *meta*-ethyltoluene **297** via *meta*-ethylbenzoic acid **298** to targeted metabolite **299** in >55% yield. This was then converted into its derivative **300** using conventional chemical techniques, for analysis and determination of absolute stereochemistry via single crystal X-ray analysis.



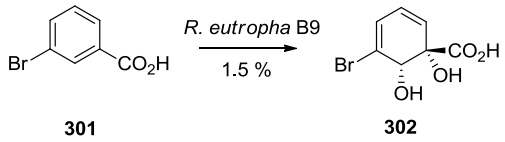
Scheme 71: Banwell 2005, one pot synthesis of chiral diene 299 with *P.putida* BGXM1.[142]

4.2 Aims and Previous work

The work presented here completes a set of studies from our previous academic report[143] which has since been compiled and published.[144]

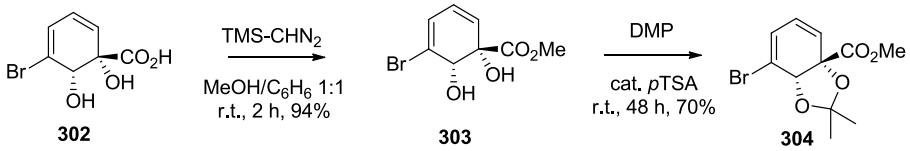
Previous studies sought to subject *meta*-bromo benzoic acid **301** to MAO, to identify and isolate enantiopure *cis*-diol diene **302**. As substituted chiral diol dienes of this origin are underexploited in synthesis, it was sought to scope the synthetic viability of possible transformations of this building block.

This present work goes further to expand the synthetic scope and viability of **302**, specifically looking at formation of tricarbonyliron(0) complexes and cross-coupling reactions.



Scheme 72: *m*-bromo benzoic acid 301 to subjected to MAO, dihydrodiol diene 302 isolated.

Our previous work[143] had successfully provided a route to bromo diene **304**, which was used at the starting point for subsequent synthetic procedures.

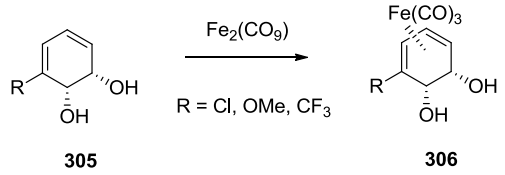


Scheme 73: Previous synthetic work [143,144]

4.3 Results and Discussion

4.3.1 Iron complexes – Relevant Literature Reports

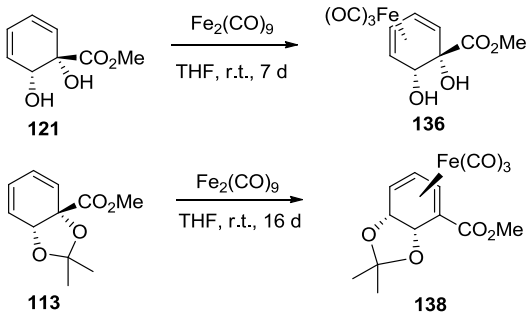
Tricarbonyl (cyclohexadiene) iron complexes were first reported by Pauson in 1958.[145] They are commonly used as intermediates in synthesis as they can 1) protect reactive diene functionality to prevent re-aromatisation 2) impart a sense of stereo control in further synthetic transformations. 3) act to separate prochiral dienes.[146] Rigid cyclohexadiene iron(0)tricarbonyl complexes have been shown to exhibit excellent stereo-induction, upon complexation.[147-149] Scheme 74.



Scheme 74: Complexation of dienes 305 with di-ironnonacarbonyl to give co-ordinated complexes 306.

Previous work within the Lewis group found that on complexation of compound **121** with di-ironnonacarbonyl a single product **136** was obtained whereby iron is co-ordinated solely to the bottom face of the diene system. This is attributed to a favourable interaction between the electron donating hydroxyl groups and the incoming 16 valence-electron iron carbonyl fragment.[68] In contrast, in an attempt to

co-ordinate iron with compound **113**, a product **138** is formed due to acetonide migration.[69]



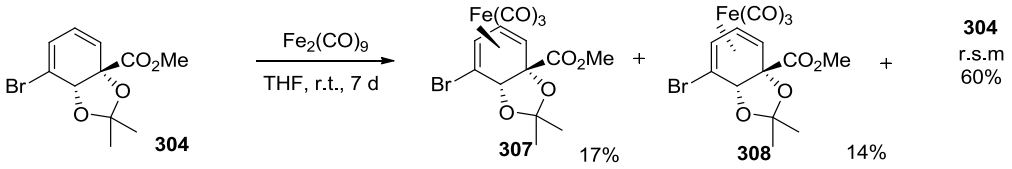
Scheme 75: Previous iron work[68,69]

It was thought that investigation of complexation of the bromo-diene compound **304** with iron might give mechanistic insight into the previous findings.

4.3.2 Iron complexes – This work

Complexation of **304** with di-ironnonacarbonyl gave a mixture of **307**, **308** and recovered starting material **304**. Scheme 76. This suggests the bromodiene is less reactive than the unsubstituted diene analogues, which furnished products in 55% yield of **136** and 26% yield of **138** (under the same reaction conditions). This could be attributed to steric clash between the incoming iron fragment and the large bromine atom.

The absolute structure of **307** was determined via X-ray crystallography. Figure 20. In contrast, compound **307** was not crystalline and proved unstable, attributed to the steric bulk of both the iron and the acetonide on the same face.



Scheme 76: Complexation of 304 with di-ironnonacarbonyl gave a mixture of 307, 308 and r.s.m.

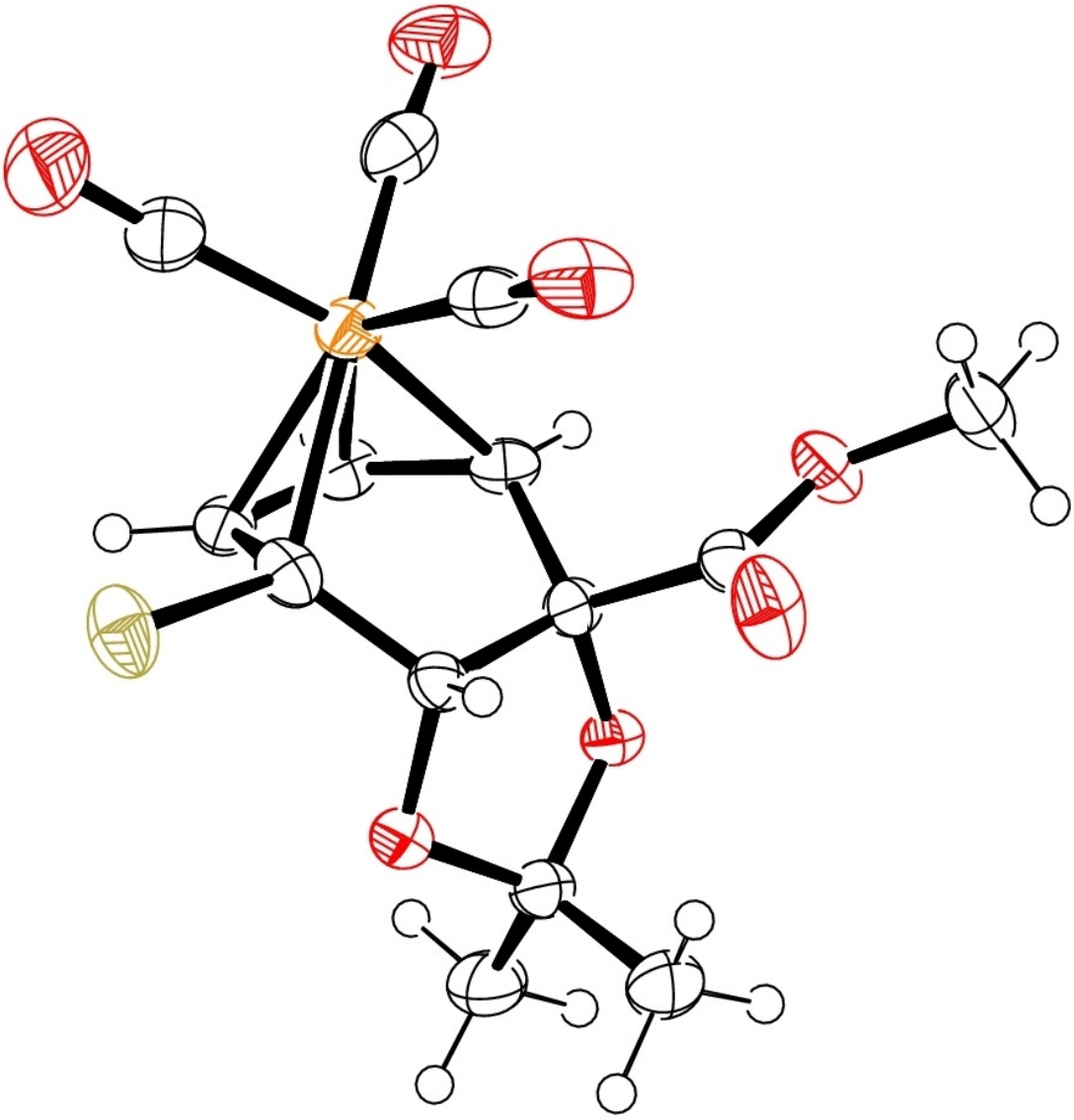
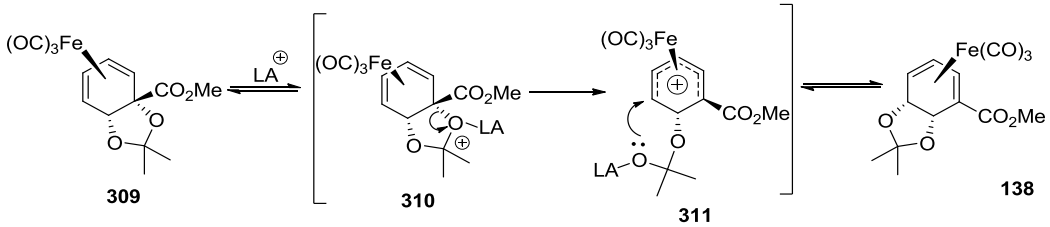


Figure 20: Solid state structure of 307. Of two independent molecules in the unit cell, only one is shown for clarity. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius.

Complexation products **307** and **308** were the only products observed; acetonide rearrangement was not observed. This supports the previously proposed mechanism for formation of **138**, namely clockwise acetonide migration. Scheme 77.



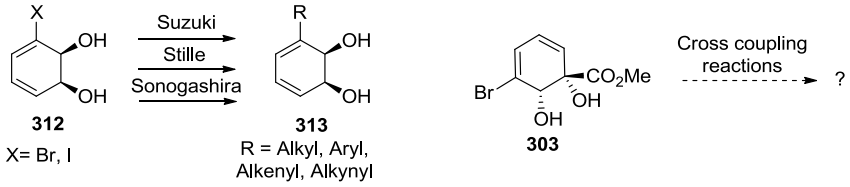
Scheme 77: Proposed mechanism of acetonide migration. [69]

In the present case, the *meta*–bromo substituent imparts steric bulk at the carbon which would be attacked by the oxygen lone pair in the acetonide migration process. The presence of the atom may play a role in blocking attack of the oxygen lone pair.

4.3.3 Cross-coupling reactions – Relevant Literature Reports

Palladium-catalysed cross-coupling reactions have been widely implemented with the more common *ortho, meta cis*-diol product from microbial oxidation, **312**.

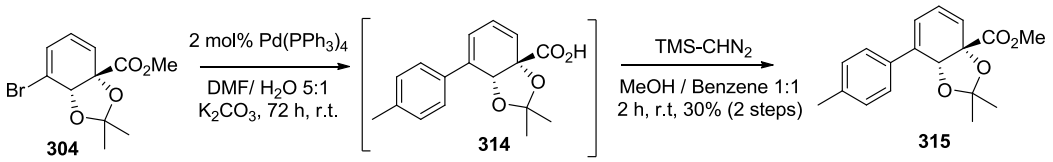
Stille cross-coupling reactions are the most prevalent within the literature,[45,150,151] with more recent examples using Suzuki cross-coupling due to their cleaner reaction conditions, avoiding the use of tin.[150-152] Songashira cross-coupling conditions have also been utilised.[25,102,152-159] Compound **302** has not previously been synthesised for synthetic purposes, therefore this work aimed to scope the possibilities of using **304** in cross-coupling reactions. Scheme 78.



Scheme 78: Previous cross-coupling chemistry

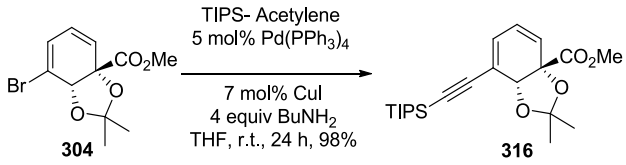
4.3.4 Cross-coupling reactions – This work

Suzuki-Miyaura coupling[160] was carried out in accordance with reported experimental procedure.[152] The desired product **315** was not observed in the first instance; however the free acid **314** was isolated and subjected to treatment with TMS-diazomethane to form the methyl ester **315** in an overall yield of 30% over two steps. Scheme 79. The free acid **314** may have formed due to the 18 equivalents of potassium carbonate used, which may result in basic hydrolysis of ester **307** to form the acid **314**.



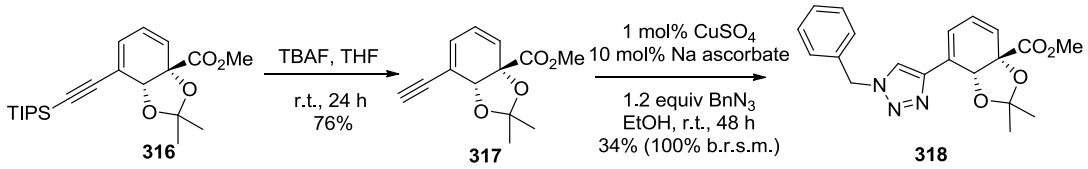
Scheme 79: Suzuki reaction to form coupled methyl ester 315.

Sonogashira coupling[161] of **304** was carried out in accordance with literature procedure [87] to give methyl ester **316** in 98%. Scheme 80.



Scheme 80: Sonogashira coupling.

It was sought to exploit further the synthetic utility of the Sonogashira product **316**. Deprotection of the TIPS silicon protecting group gave the terminal acetylene **317**. This was then subjected to copper catalysed Huisgen[162] cycloaddition with benzyl azide to form a 1,2,3-triazole, **318**. These reactions, commonly referred to as an example of 'click reactions' are known to proceed in high yields. Scheme 81.



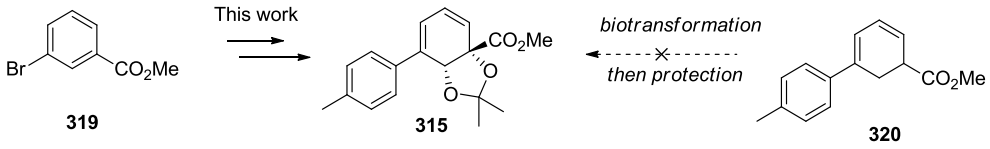
Scheme 81: Azide click cycloaddition

4.3.5 Conclusions

This expansion of previous work has shown that the bromo-diene **304**, although less reactive than its un–substituted counterpart **121**, can co-ordinate to form iron complexes. The bromo complex does not rearrange which supports the proposed mechanism from previous work.[69]

This work has also demonstrated the synthetic utility of the bromine substituent as a synthetic handle in cross-coupling reactions. Both Suzuki and Sonogashira coulplings have proven successful with moderate to excellent yields. Further expansion with azide 'click' chemistry illustrates the synthetic utility and stability of the compound, enabling diversification to other chemical intermediates.

The formation of cross-coupling products especially **315** is of particular significance, as these structures are arene dihydrodiol derivatives that would not be accessible by direct metabolism of the corresponding arene substrates. Scheme 82.

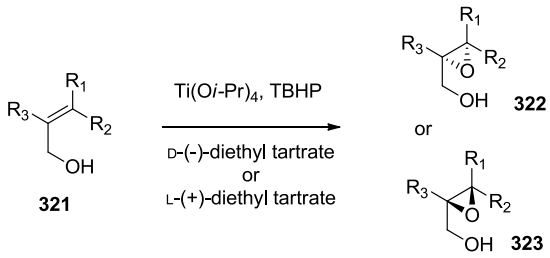


Scheme 82: Dihydrodiol product 315 synthesised via this work, potentially inaccesible dihydroxylation product of 320.

5 Chapter 5: Introduction Asymmetric Epoxidations

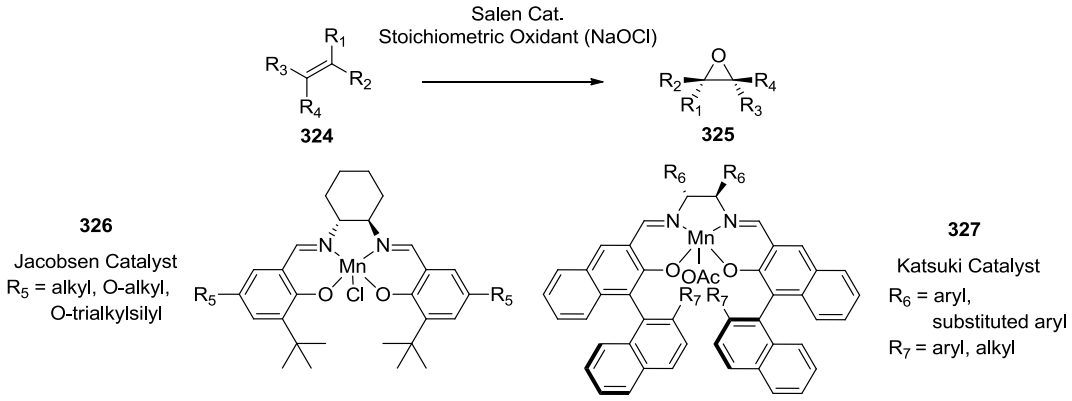
5.1 Background to Asymmetric Epoxidations

Catalytic asymmetric epoxidations are an important class of chemical transformation as they enable the generation of up to two stereogenic centres and a reactive epoxide which can be further functionalised. This enables such methodology to be used towards the synthesis of enantiomerically pure chemical building blocks for the synthesis of complex biologically active molecules.[163] The importance of this transformation was most notably recognised by the Nobel Prize in chemistry from 2001, awarded for asymmetric catalysis, where Sharpless (one of three winners) gained recognition for his work towards directed asymmetric epoxidation catalysis. Sharpless' and Katsuki's seminal work employed $Ti(O^iPr)_4$ as the transition metal catalyst precursor, TBHP (*tert*-butyl hydrogen peroxide) as the oxidant and DET (diethyltartrate) as the chiral additive, achieving >90% *ee* on allylic alcohol substrates **321**. [164] Scheme 83.



Scheme 83: Sharpless asymmetric epoxidation.[164]

The use of chiral titanium complexes, developed by Sharpless has seen much innovation, development and progress since his initial work in the 1980s. This area has been extensively reviewed.[165] This work has been followed by the next significant milestone, development of manganese-salen complexes by Katsuki *et al.*[166] and Jacobsen *et al.*[167] Scheme 84.



Scheme 84: Jacobsen and Katsuki's catalyst.

Jacobsen and Katsuki showed the enantioselective epoxidations of unfunctionalised alkyl- and aryl- substituted olefins. The catalysts show strong structural resemblance to porphyrin-metal complexes that are known in biological systems. The procedure showed excellent enantioselectivities for specific substrates with values 90 – 95% *ee.*[166]

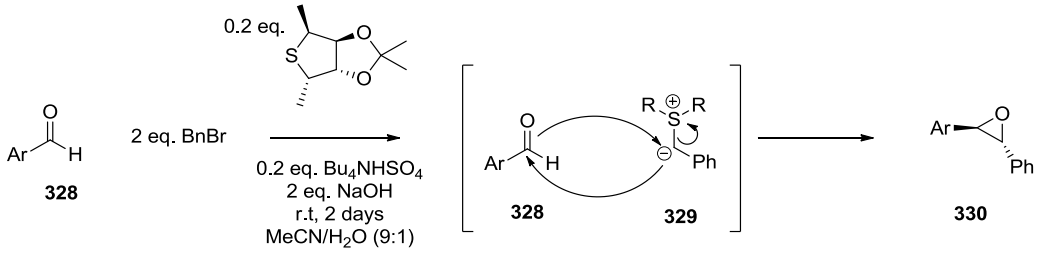
The advantages of the Jacobson-Katsuki epoxidation are: [168]

1. Chiral Schiff-base salen ligands are easily synthesised via the condensation of readily available C_2 symmetric chiral diamines and substituted salicylaldehydes
2. Expands the substrate scope from Sharpless' allylic alcohols to a variety of conjugated, non-conjugated, substituted and functionalised alkenes.
3. Cyclic and acyclic (*Z*)-1,2-disubstitued alkenes are epoxidised with almost 100% enantioselectivity.
4. (*E*)-1,2-disubstitued oelfins are poor substrates for Jacobsen's catalyst **326**, but work better with Katsuki's **327**.
5. Cheap and readily available stoichiometric oxidants can be used e.g. NaOCl, *m*CPBA and PhIO.

5.2 Organocatalytic Asymmetric Epoxidation

From a sustainability perspective organocatalysis can be viewed to be beneficial as it eliminates the use of metals, which (depending on the metal) could be scarce, toxic, and expensive or require extensive processing, mining or catalyst and ligand synthesis.

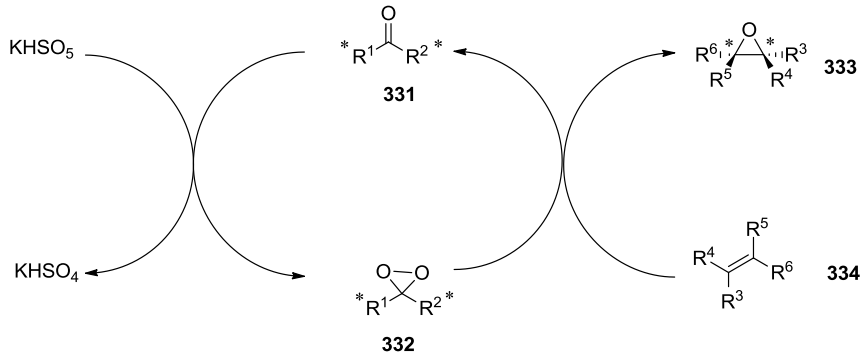
A metal free epoxidation example is that from Corey and Chaykovsky,[169] who in 1962 developed methodology for the generation of epoxides from the corresponding aldehydes or ketones **328**. A reactive sulfur ylide **329** is prepared *in situ* from deprotonation of the corresponding sulfonium salt.[170] Development has shown that the use of chiral sulfides in asymmetric epoxidations is possible.[171,172] An example is from Metzner *et al.,* who developed a new generation of 2,5-dimethylthiolanes with a locked conformation to promote the asymmetric addition of chiral sulfonium ylides to aldehydes. The novel chiral sulfur derivative succeeded in the synthesis of *trans*-stilbene oxide derivatives with enantiomeric ratios ranging from 90 – 96% *ee*.[171] Scheme 85.



Scheme 85: Metzner *et al.*[171] Asymmetric epoxidations using chiral sulfur ylides.

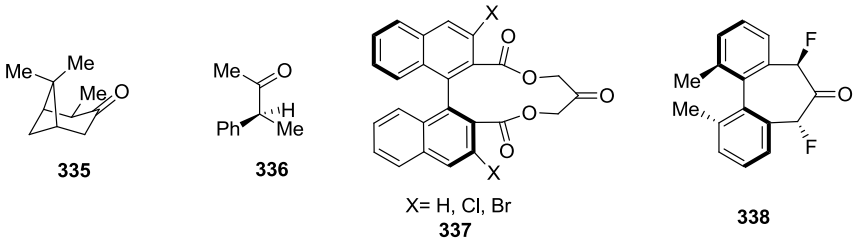
5.2.1 Chiral Ketones

The use of chiral ketones **331** in the presence of Oxone® (K_2SO_4, $KHSO_4$ and $KHSO_5$) generates chiral dioxiranes **332**, which are capable of oxidising alkenes to form the corresponding epoxides **333**, regenerating the chiral ketone **331**. For this reason dioxiranes are considered to be environmentally friendly and versatile oxidizing agents. Scheme 86.



Scheme 86: Generic oxidation of alkenes by chiral dioxiranes generated *in situ* from chiral ketone and Oxone.

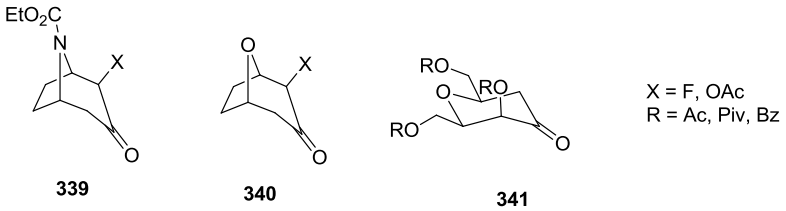
In the seminal publication of Curci *et al.,* in 1984 [173] the first chiral ketone catalysed asymmetric epoxidation was reported. Epoxidation of 1-methylcyclohexene and trans-β-methylstyrene with chiral ketone **335** and **336** in biphasic systems led to good yields and up to 12.5% *ee.* Later in 1996, Yang [174] exploited the use of binapthylene chiral ketones **337**, with intention of the C_2 symmetry aiding selectivity and activity of the catalyst. The electron withdrawing nature of **337** enabled it to be an effective catalyst, with high conversions obtained at 10 mol%. It was found that increasing the size of the *para* substituent of *trans* stilbenes substrates improved the selectivity from 47 to 87% *ee*. Following on from Yang's work many other C_2 symmetric biphenyl ketones have been evaluated, including the work of Denmark *et al.,*[175] who developed 7 membered biaryl ketone **338** to achieve good yields and selectivities up to 94% *ee* for *trans* stilbene. Scheme 87.



Scheme 87: Examples of Chiral Ketones for Epoxidation of Alkenes

In 1998, Armstrong and co-workers reported bicyclic ketones **339 – 341** to be used with Oxone to enantioselectivley epoxidise a variety of alkene substrates. Scheme 88.[176,177] Catalyst **339** achieved 83% *ee* for a variety of substrates. Replacing the nitrogen bridge head with oxygen, **340**, lead to further improvements, up to 98% *ee,* with acetate substituents giving the best selectivities in both cases. More

recently Armstrong has investigated a new class of tetrahydropyran-4-one catalysts.[178] Catalyst **341** was considered to be more stable than the bicyclic counterparts, with as low as 10 mol% being used to obtain 100% conversion. Despite slightly lowered enantioselectivities (43 to 83% *ee*) compared to the bridged bicyclic systems, this suggests that this bridge within the structure does not contribute greatly to the observed enantioselectivity. However Armstrong concluded that the α-acyloxy group seemed to play an important role in reactivity and selectivity.

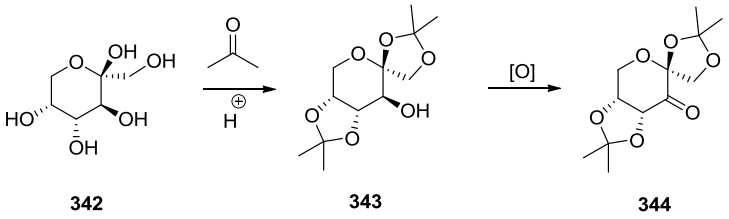


Scheme 88: Armstrong's catalysts.[176-178]

Undoubtedly the most well-known organocatalytic asymmetric epoxidation is the work of Shi *et al.*[173,179-181] Shi and co-workers developed a range of chiral ketones derived from sugars. The easily synthesised catalysts are now commercially available and have been employed in the synthesis of natural products.[182]

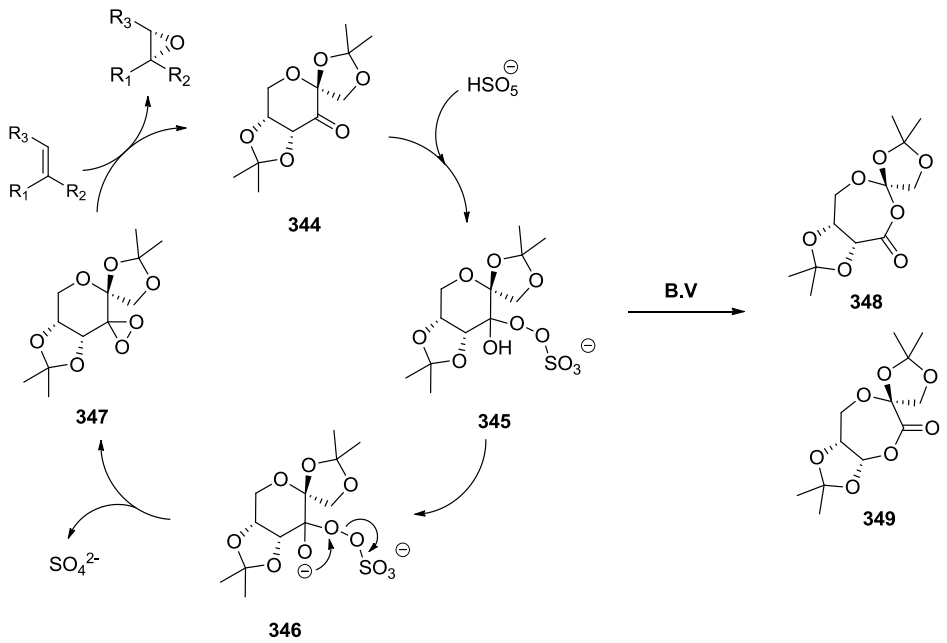
Shi's principal catalyst **344** was synthesised from D-fructose **342**, with the other enantiomer easily accessible from L-sorbose which can be converted into L-fructose, this method avoids incurring excessive cost of using L-fructose directly.[183] The catalyst **344** was designed based on three key principles[179]

1. The stereogenic centres are close to the reacting centre, resulting in efficient stereochemical communication between substrate and catalyst.
2. The presence of the fused ring and quaternary centre α to the carbonyl group minimises the epimerisation of the stereogenic centres.
3. One face of the catalyst is sterically blocked to limit the possible competing approaches.



Scheme 89: Synthesis of Shi catalyst from fructose.

It was found that pH has a large impact on the epoxidation reactions. [180] Earlier studies were carried out at pH 7 – 8 in an attempt to reduce the decomposition of Oxone, however this resulted in the decomposition of ketone catalyst **344**, and formation of assumed byproducts **348** – **349,** most likely due to Baeyer – Villiger oxidation. (N.B. byproducts **348** and **349** were never isolated from this reaction, attributed to their decomposition on work up and affinity to remain within the aqueous phase, identification of byproducts was investigated under controlled reaction conditions. Scheme 92.) The optimal pH of 10.5 was achieved with addition of K_2CO_3 and saw conversion increase from 5% to >80%, this was attributed to the improved formation of anion **346** and subsequent formation of the dioxirane **347** within the catalytic cycle. [184] Scheme 90.



Scheme 90: Mechanism of the Shi epoxidation, and possible decomposition products.

Exploring the substrate scope of Shi catalyst 344, unfuctionalised *trans* and tri substituted olefins, as well as allylic, homoallylic, conjugated dienes, silyl enol ethers and esters were investigated. This shows broad substrate scope and good functional group tolerances.
Table 3.

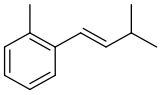
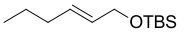
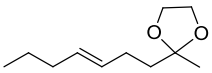
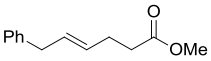
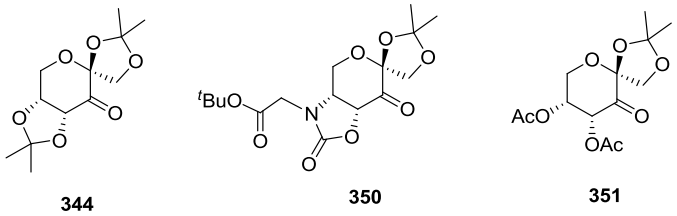
Entry	Substrate	Yield (%)	*ee* (%)
1		85	98
2		78	96
3		83	95
4		92	92
5		68	92

Table 3: Asymmetric epoxidation of trans and trisubstituted olefins with Shi catalyst 344. Reagents and conditions: Ketone (0.3 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN-DMM-0.5 M $Na_2B_4O_7 \cdot 10H_2O$ of aq Na_2EDTA (1:2:2 v/v).

The high catalyst loadings are attributed to the competing Baeyer – Villiger decomposition pathways. Scheme 90. In attempts to reduce this, several different catalyst iterations and designs have been investigated. [184] Scheme 91.



Scheme 91: Different generation of Shi chiral ketone catalyst.

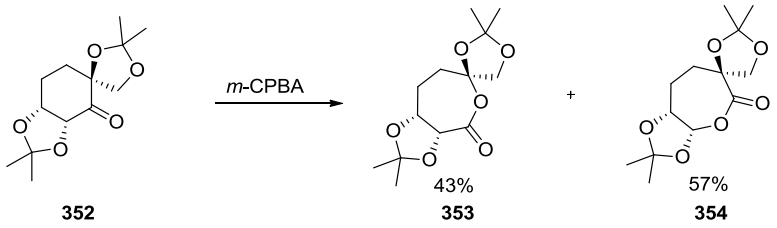
Catalyst **350** with the fused oxazolidinone imparted enhanced electron withdrawing characteristics, enabling catalyst loading to be reduced to 1 – 5 mol%. Since dioxiranes are electrophilic reagents acetate derived catalyst **351** proved to be an efficient catalyst for electron deficient α,β- unsaturated ketones, 57% – 96% yield and 82% – 97% *ee*, an improvement from the original catalyst **344**. Scheme 91.

5.2.2 Chiral Carbocycles Ketone Catalysts

As this thesis concerns carbocyclic compounds, (aminocarbasugars and cyclitol chapter) it is interesting to note the variety of carbocycle research which followed from Shi's seminal publications.

In 2001 Shi investigated carbocyclic chiral ketones derived in 10 steps from from (–)-quinic acid; these included the carbocyclic analogue **352** to the original Shi catalyst **344**. [185] Scheme 92. Shi noted that the most dramatic effect of replacing the pyranose oxygen with CH_2 was the decrease in reactivity. Catalyst **352** gave <10% conversion in 8 h of *trans*-stilbene, compared to 75% conversion in 1.5 h for the Shi Catalyst **344**. This indicated that the pyranose oxygen is beneficial for the reactivity, the electron withdrawing nature inductively activates the carbonyl to attack from the Oxone, and further activates the electrophilic dioxiranes to attack from the alkene substrate.

Additionally under controlled oxidative Baeyer – Villiger reactions, it was found that carbocycle ketone **352** formed substantial amounts of the corresponding lactones **353** – **354**, suggesting the CH_2 enhances the relative migratory aptitude of the spiro carbon.



Scheme 92: Shi carbocyclic chiral ketone. [185]

Structural X-Ray analysis of **352** indicated slight differences in conformational shape compared to the original catalyst, destabilizing steric interactions were discussed as an explanation for decreased activity of catalyst **352**. Figure 21. It was also noted that carbocyclic ketone **344** gave higher *ee*'s for *cis*-olefins indicating a different type of olefin requires different structural elements for stereoselectivity.

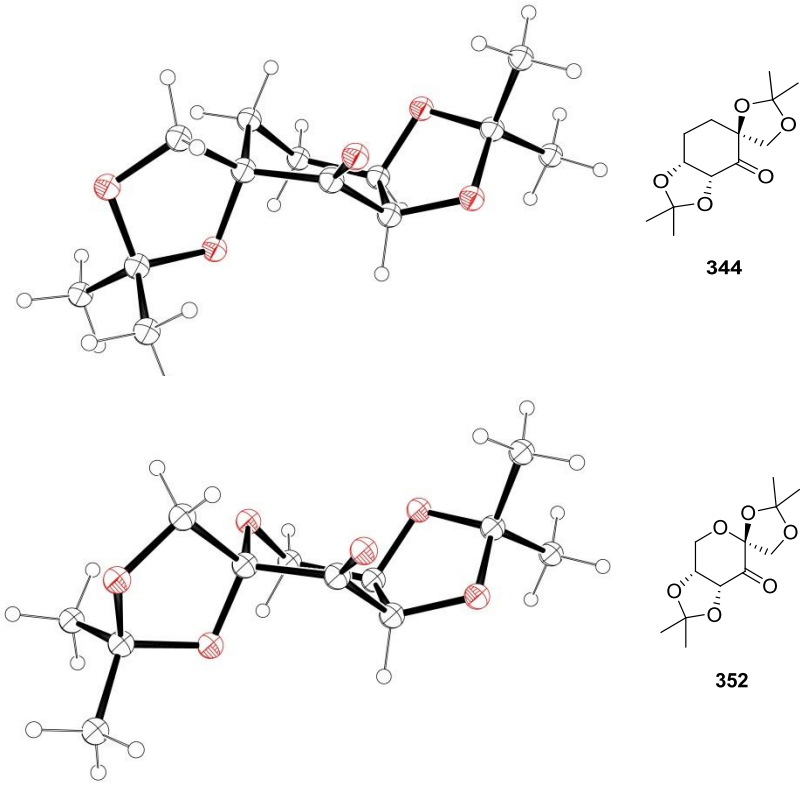
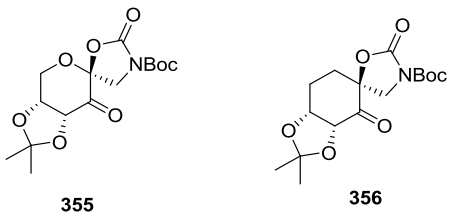


Figure 21: X-ray structures of ketone 344 and 352. Structures taken from [185]

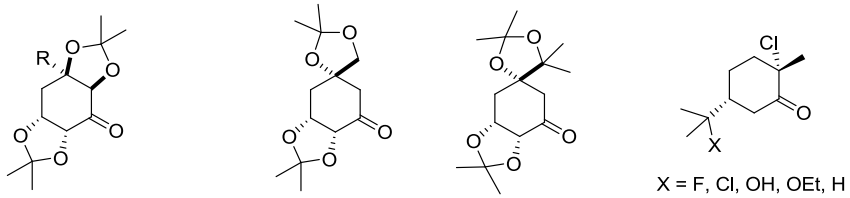
Following this, in 2004 Shi presented a direct comparison and study on transition states for chiral ketones **355** and **356**.[186] Scheme 93. Ketone **356** was found to be an active catalyst for the styrenes, ((*R*)-styrene oxide was obtained with 20 mol% **356** at -10 °C over 8 h which gave 100% conversion and 90% *ee*). Higher ee's obtained with carbocycle **356** rather than **355** were attributed to the replacement of the pyranonse oxygen with CH_2. Experiments probed the substrate structures and suggested favourable transition states and corresponding favourable orbital interactions to explain observed selectivities of this challenging class of styrene substrates.



Scheme 93: Shi carbocyclic ketone 356, compariative study to pyranose 355.

Further carbocyclic ketone structures have been investigated for their epoxidation capabilities, including structure **357**, and its derivatives.[187,188] Investigation into this

class of C_2 symmetric ketones highlighted the importance of ketone conformation in reactivity and selectivity of the catalyst. Scheme 94.



357 358 359 360

Scheme 94: Carbocyclic ketone catalysts.

During investigations into the position of the spiro structural element in the carbocycle ketones, Shi evaluated the reactivity and selectivity of structures **358** – **359**.[185] Results indicated lower enantioselectivities (12% – 72% *ee*) for a variety of test substrates, indicating that the chiral control element should be close and big enough to impart good *ee*s but not too much so as to retard the reaction. Scheme 94.

Further investigations in 1998 by Yang *et. al.,* [189] reported a series of ketones **360** containing a quaternary carbon adjacent to the ketone and various substituents on the ring. The work aimed to investigate the remote substituent effect and electronic tuning potential as an important tool in catalyst design. Following Shi's Oxone procedure, Yang reported epoxidation of various *meta* or *para* substituted *trans*-stilbenes achieving selectivities 42% - 97% *ee*. Scheme 94.

To conclude this section, it is obvious from the amount of literature available, that cyclic ketones provide viable asymmetric organocatalytic systems for the epoxidation of a range of alkene substrates.[184,190]

5.3 Organocatalytic Asymmetric Epoxidations – with H_2O_2

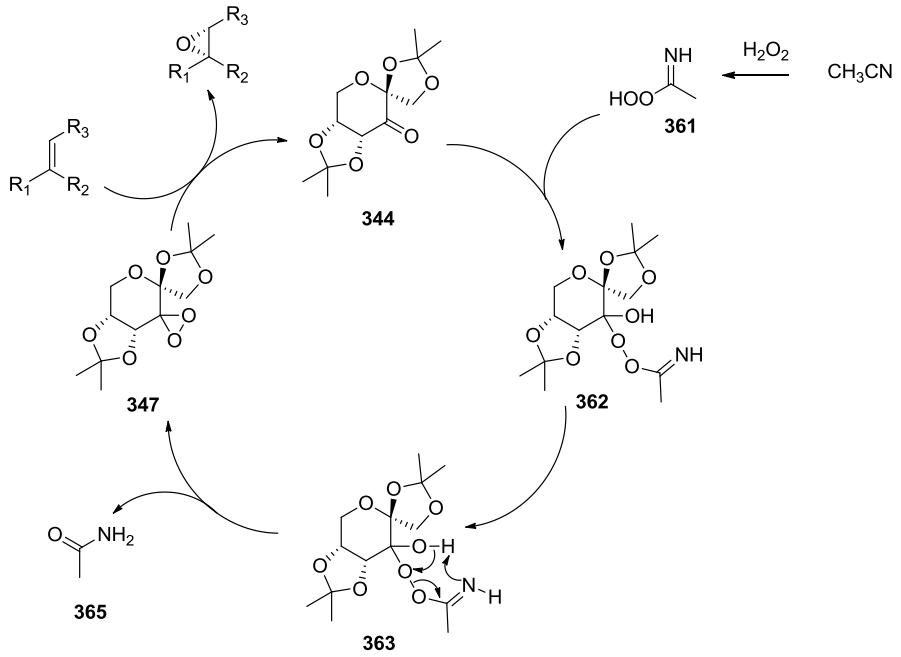
With an interest in organocatalytic asymmetric epoxidations which utilise hydrogen peroxide, this area has been extensively reviewed.[163,184,191,192] Hydrogen peroxide as oxidant is becoming increasingly utilised as a reagent due to its environmental and economic benefits, thanks to high atom economy and formation of water as a by-product.[192] Organocatalysis has emerged as a convenient and effective tool for

stereoselective synthesis of either simple or complex molecular scaffolds. An organocatalyst presents many benefits as an alternative to traditional metal catalysed reactions – since generally they are easily available, generally derived from the chiral pool, and are less sensitive to moisture and aerobic conditions. [192]

Within this section key epoxidations which utilise hydrogen peroxide that have specific relevance to the work carried out within this thesis will be reviewed.

5.3.1 Shi – Chiral ketones and H_2O_2

From the previous section it has been shown that the most effective and widely employed ketone based catalysis methodology comes from Shi and Yang, whom developed original Oxone (K_2SO_4, $KHSO_4$ and $KHSO_5$) methodology of generating dioxiranes *in situ* for the epoxidation of alkenes. In more recent work, 1999 – 2007,[193-195] Shi developed the methodology to use peroxymic acid **361** formed *in situ* from hydrogen peroxide and acetonitrile. (analogous to the Payne oxidation [196]) Scheme 95. Under the hydrogen peroxide conditions the chiral Shi catalyst **344** was able to epoxidise *trans*–stilbene in 24 h with 90% yield and 98% *ee.*



Scheme 95: Shi epoxidations Utilising hydrogen peroxide.

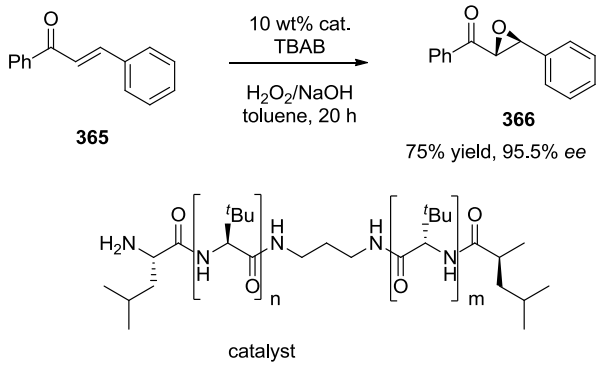
These modified reaction conditions proved to be milder, reducing the amount of salts and solvents needed and eliminating the need for the use of parallel syringe

pumps and careful addition of reagents. Results were comparable to that of the Oxone based systems. Mixed solvent systems proved useful with substrates of poor solubility, with efficient mixing being noted as being influential in achieving good yields in the biphasic system. Various nitriles were evaluated, with acetonitrile being optimal. [193]

5.3.2 Juliá Colonna – Peptide Asymmetric Epoxidations

The Juliá–Colonna epoxidations from the 1980s [197-199] is the peptide catalysed asymmetric epoxidations of enones. The methodology utilises a three phase system consisting of aqueous NaOH, hydrogen peroxide, toluene and insoluble peptide, typically poly-L-alanine or poly-L-leucine as catalysts to convert α,β-unsaturated ketones to their corresponding epoxides in good yields and high enantioselectivities.

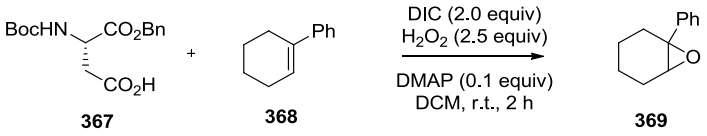
A recent review highlights the use of ^{t}Bu-glycine in the enantioselective epoxidation of substrate **365.**[200] Scheme 96.



Scheme 96: Juliá–Colonna epoxidations. [200]

5.3.3 Miller – Peptide Asymmetric Epoxidaitons.

Following on from the peptide theme, Miller *et al.* [201-204] developed an *N*-Boc-protected L-aspartate benzyl ester **367** in combination with DIC as a stoichiometric activator, DMAP as an acyl transfer catalyst and hydrogen peroxide. Reactions on 1-phenylcyclohexene **368** were performed in order to optimise epoxidation conditions achirally with up to 15 catalytic turnovers (5 mol% cat. leading to 74% yield within 3.5 h). Scheme 97.



Scheme 97: Miller's optimised reaction conditions.

Miller performed numerous experiments to establish the role of each of the components of the reaction mixture. As a result of the findings, a mechanism was proposed. Figure 22.

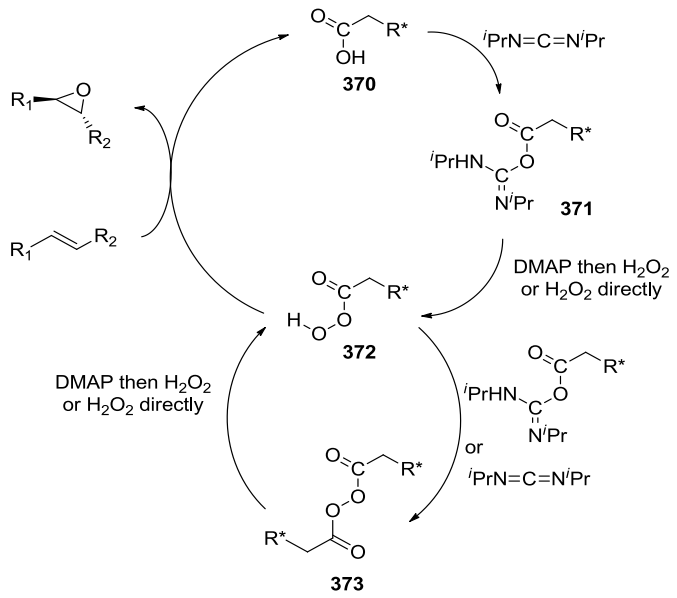
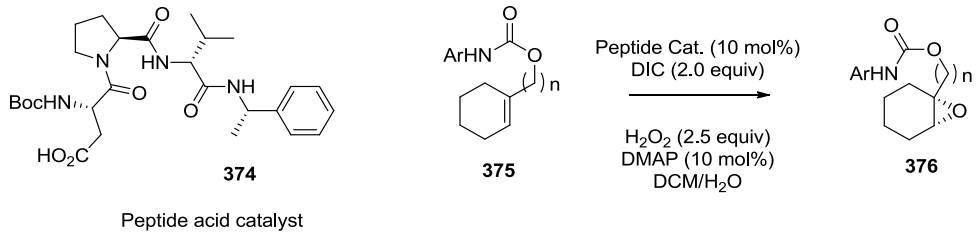


Figure 22: Miller's proposed mechanism. R* = chiral side chain.

Miller suggested that as expected from the literature precedent[205,206] diacyl peroxide byproduct **373** is formed under the reaction conditions. Formation of **373** is obviously undesirable, as competes with the epoxidation process and is only slowly perhydrolysised back to **372**. Miller found that addition of DMAP accelerates the perhydrolysis reaction. Critically Miller stated that no conversion of **368** to **369** was observed until addition of peptide catalyst **367**.

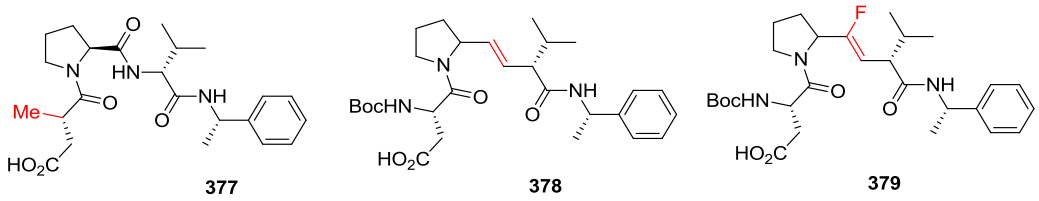
To induce asymmetry, aspartic acid was incorporated into a peptide sequence which resulted in a β-turn-type structure as shown in peptide catalyst structure **374**. To test the epoxidation capabilities of peptide **374** carbamate functionalised substrates **375** were chosen to facilitate potential catalyst–substrate interaction through hydrogen bonding. Scheme 98.



Scheme 98: Miller's peptide catalyst and substrate reaction conditions.

Results indicated that **374** was a suitable catalyst obtaining 17 catalytic turnovers at 25 °C. Substrate (Ar = Ph, n = 1) could be epoxidised obtaining 97% yield and 89% *ee* at -10 °C. Various other carbamate substrates were tested the majority with high yields and selectivities, albeit in some examples at low temperature and over extended periods of time.

In a follow up study, [204] catalyst analogues **377** – **379** were assessed for their catalytic activity, to give insight and mechanistic understanding.



Scheme 99: Miller's new catalysts [204]

Catalyst **377** gave insight into the importance of the NHBoc functionality; under standard test conditions catalyst gave 88% *ee* which is comparable to the original catalyst **374**, which suggests the NHBoc group is not involved in the hydrogen bonding interaction with the substrate. Catalyst **378** evaluated the function of the Pro-D-Val amide, which in this case was replaced by an alkene, the reduction in selectivity was observed, 16% *ee,* under standard conditions, which suggests this structural feature contributes greatly to the observed enantioselectivity. This is also supported by the observed structural differences in the X-ray crystal structures. Finally fluorinated alkene catalyst **379** was used to imitate amide like character in an olefinic mimic. Enatioselectivities observed with **379** were 52% *ee*, explained by a slightly weaker hydrogen bonding effect, with 'inbetween' characteristics of the two previous catalysts **377** and **378**.

5.4 Summary

From this short yet specific literature review it is firstly obvious that there is a wealth of work and research in the area of asymmetric epoxidations.

The majority of the asymmetric organocatalytic epoxidations – for this is the area of research interest – employ catalysts which are derived from natural sugars or chiral pool sources.

We have seen in the preliminary introduction that MAO offers viable route to an abundant source of enantio-pure chiral material. It is therefore intuitive to explore the viability of MAO products to the application of asymmetric organocatalytic epoxidations.

6 Chapter 6: Peracid Epoxidations

6.1 Introduction – Chiral peracids & epoxidations.

This body of work takes its inspiration from Miller *et al*.[201] who utilised hydrogen peroxide and a chiral peptide catalyst **374** to selectively epoxidise specific alkenes **380** which contain a carbamate side chain. Their report presents varying enantiomeric excesses and conversions over a variety of time periods and temperatures, including some excellent results, and highlights the potential of a chiral acid, standard peptide coupling reagents and hydrogen peroxide to generate selective epoxides **381** under the conditions of asymmetric catalysis.

Figure 23.

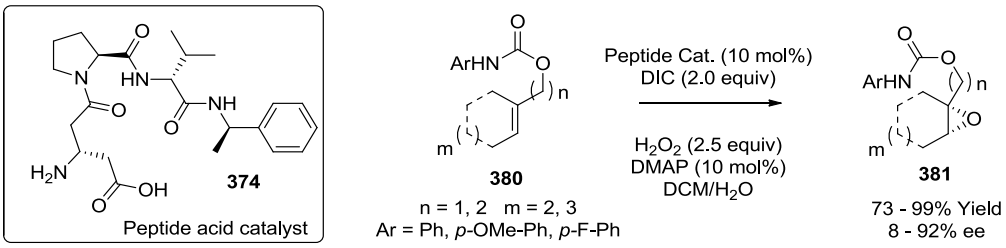


Figure 23: Miller's chiral acid peptide acid method.

With access to a sustainable source of a chiral acid **30**, via the MAO of benzoic acid, we sought to scope its viability as a catalyst for the asymmetric epoxidations of alkenes with hydrogen peroxide. Figure 24.

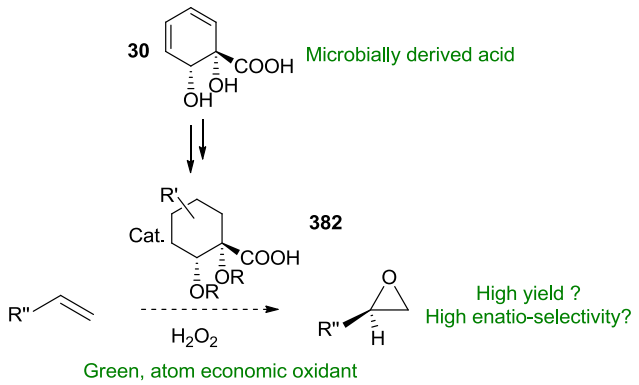


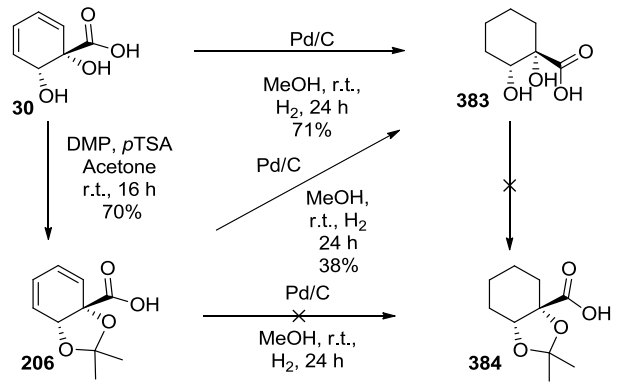
Figure 24: Aim of microbial derived acid to act in epoxidations reactions.

The initial aim of this work was to synthesise acid structure of type **382** to be used as catalysts for the enantioselective epoxidation of alkenes. It is necessary to protect the alcohol functionalities so they do not interfere with the coupling reagents and self-condense. Additionally removal of the reactive diene functionality is essential so the catalyst does not affect self-epoxidation.

6.2 Results and Discussion: Catalyst Synthesis

6.2.1 Acetonide protection of diol acid.

Initially we sought to protect the diol **30** utilising standard acetal protection, a common technique used for this type of compounds, having precedent within the research group.[68,69,72,75,76,144,207] Scheme 100.



Scheme 100: Acetonide Protection hydrogenated diol acid.

Starting with the product from MAO **30**, hydrogenation with palladium on carbon gave the desired saturated acid diol **383**, albeit obtained with varying yields, 33-71%. Higher isolated yields were obtained with an adapted column chromatography purification procedure; addition of 10%, 50% v/v aqueous AcOH, to the corresponding eluting solvent prevented compounds adhering and retaining on the column resulting in higher isolated yields. Residual AcOH could be removed from the isolated final compound under reduced pressure and heating to obtain pure, white crystalline product **383**.

The diastereoisomer of **383** has been previously synthesised, with coincidentally consistent melting points to the product synthesised here. [208,209]

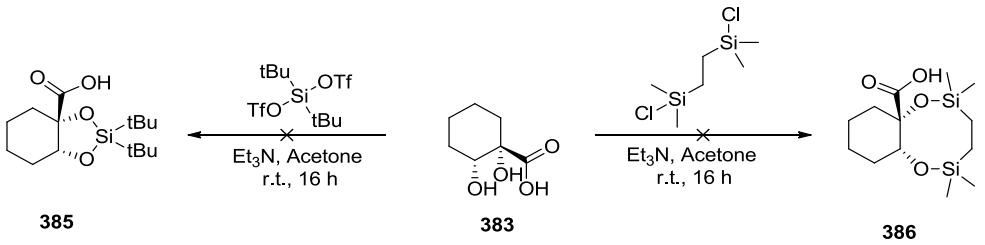
Attempts to form the acetonide protected product **384** were unsuccessful. Conditions included both the standard 2,2-Dimethoxypropane and *p*TSA,[207] Zerolit 225 solid acid resin, heating and varying solvents, all resulting in recovery of starting material **383**.

In an alternative approach, taking the known acetonide protected diene **206**, under standard hydrogenation conditions, the desired product **384** was not formed, instead the product isolated, **383**, indicated acetonide deprotection.

We can attribute the instability of compound **384**, and the inability to form the acetonide group to the inherent acid sensitivity of an acetal protecting group. With the presence of the free carboxylic acid functionality on the molecule itself, deprotection could plausibly be autocatalytic.

6.2.2 Silicon protection of diol acid.

With an abundance of the hydrogenated diol acid **383**, silicon protection and formation of bicyclic systems were attempted. More rigid structures may possibly induce enhanced enantioselectivity if used as catalysts. Scheme 101. Following procedures common within the literature for silicon protection,[210] attempts using Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) and 1,2-bis(chlorodimethylsilyl)ethane under standard silylation conditions to form the corresponding desired products **385** and **386** were unsuccessful. Again this could conceivably be attributed to the acid lability of silacycles **385** and **386**, especially steric strained disiloxane **385**.



385 383 386

Scheme 101: Silicon protection of diol acids.

6.2.3 Formation of acid catalysts via esters

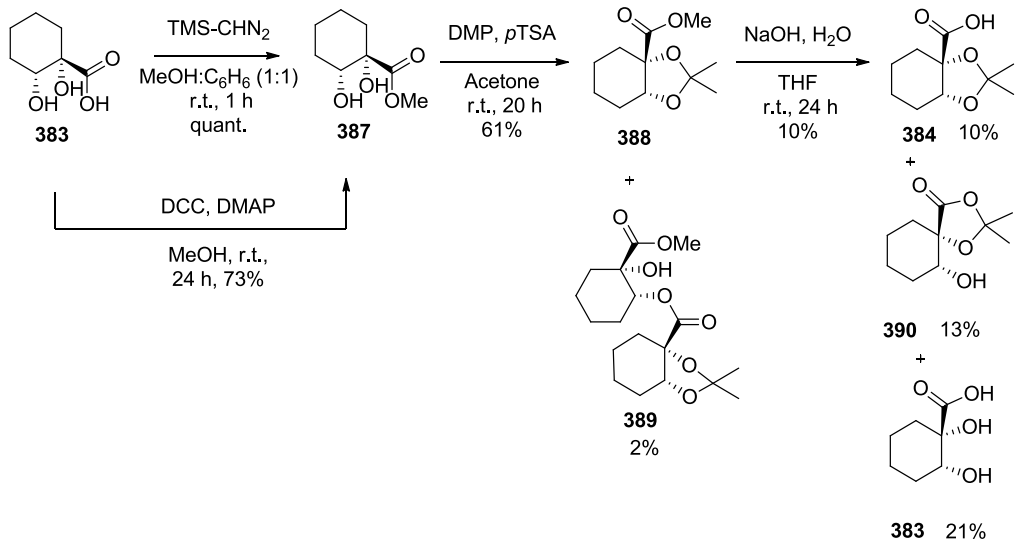
With problems of autocatalytic deprotection due to the presence of the free acid functionality we sought to transiently protect the acid as an ester. Esters are formed readily and are much simpler to purify.[76,144] Scheme 102.

6.2.4 Formation via methyl esters

Formation of the methyl ester **387** using TMS diazomethane proceeded under quantitative conversion. Surprisingly, alternative use of dicyclocarbodiimide (DCC), avoiding both cost and toxicity of TMS diazomethane, proceeded well with yields 53-73%. No self-coupled dimer products were observed, despite the alcohol functionality in the starting material. This could be attributed to the dilute reaction conditions; there is more chance of a compound coupling with methanol than with another molecule of itself.

Methyl ester **387** has been previously synthesised albeit not in 100% *ee*, but as a scalemic mixture [211,212]

Acetonide protection of methyl ester **388** proceeded well with 61% yield to give the desired product. On a large scale repetition of this procedure a byproduct **389** was identified isolated in a 2% yield. This dimer formation, due to reaction with the starting material **387** with the desired product **388** highlights the potential unwanted reactivity of the secondary alcohol.



Scheme 102: Formation of acids via methyl esters.

The final basic hydrolysis step of methyl ester **388** proved problematic. LiOH was unsuccessful and several attempts using NaOH and THF both at room temperature and heating gave inconsistent results with yields ranging from 5 to 10%. Under reflux both decomposition and rearrangement was observed giving acetonide migration product **390** 13%, desired acid **384** 10% and decomposition product diol acid **383** 21%. Reduction in isolated mass could be attributed to loss of product in the aqueous acidification and workup. These results indicate the sensitive nature of the acetonide with regards to unwanted migration and cleavage.

The Migration product **390** was fully assigned by detailed 2D-NMR spectroscopy studies, as described below. Analysis of ^{1}H and ^{13}C 1D-NMR spectra alone were insufficient, with only a few assignments being made. Figure 25.

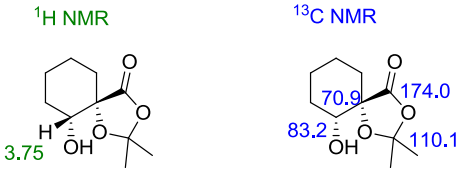


Figure 25: NMR spectroscopy assignments based on complete 2D data.

Analysis of HSQC identified direct C-H bond interactions; this enabled the complex aliphatic region of the spectra to be split up to single proton environments. Additionally the OH region was identified. Figure 26. This technique alone was insufficient for further assignments to be made.

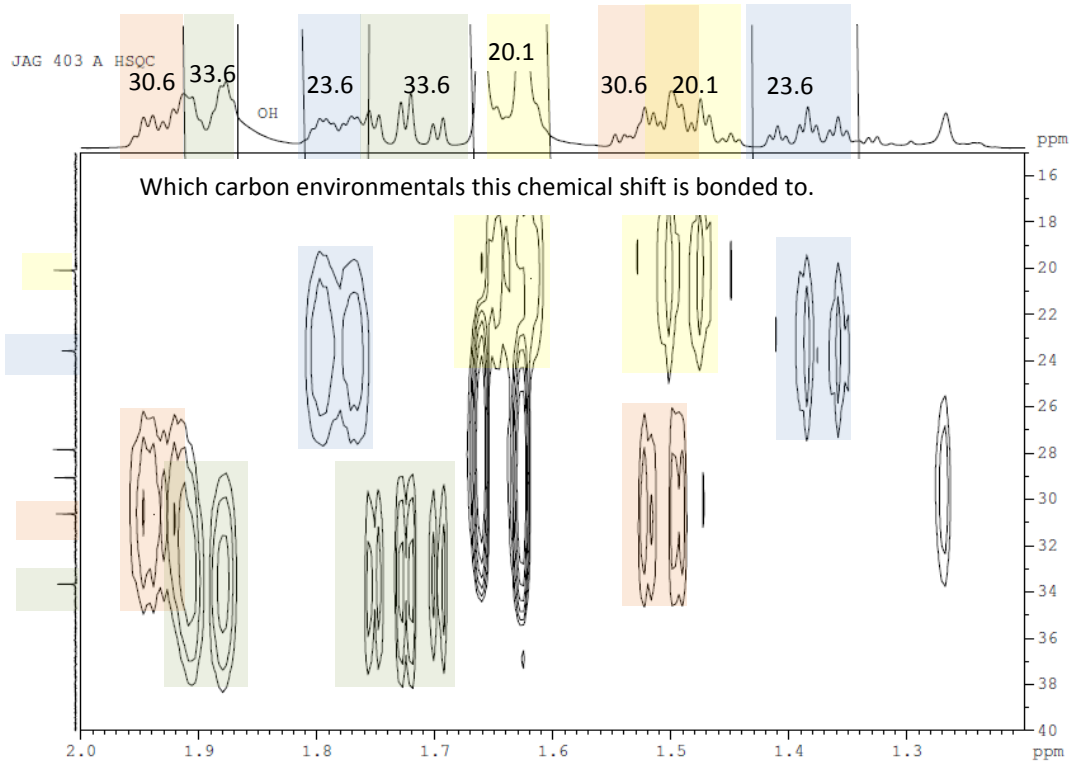


Figure 26: Compound 390 HSQC 2D-NMR Spectra, indicating which protons are bound to each carbon resonance.

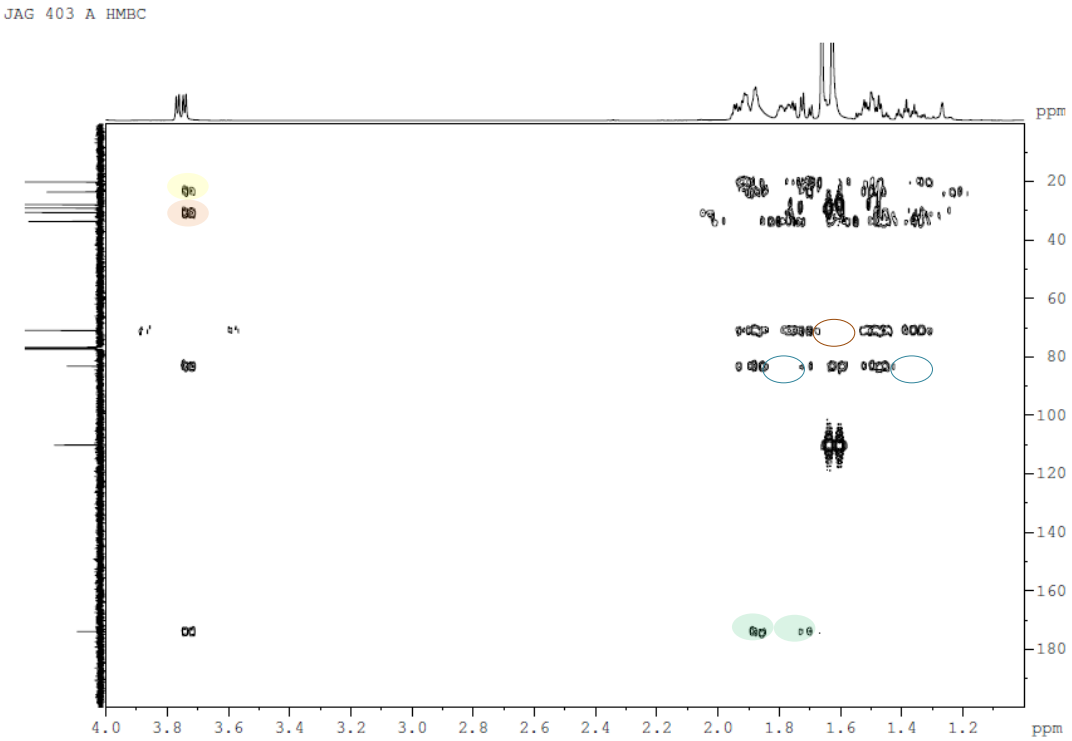


Figure 27: 390 HMBC 2D-NMR Spectra

Complete assignment was achieved with combined analysis of both HSQC and HMBC 2D-NMR spectra. HMBC indicated the carbonyl δ_c 174.0 interacted with saturated hydrogens at δ_H 1.92 and 1.73. HSQC could identify that these hydrogens were bonded to δ_c 33.6. Figure 28.

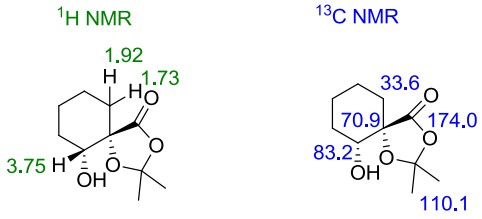


Figure 28: Further assignments of compound 390 via interpretation of 2D-NMR spectra.

Analysis of HMBC δ_H 3.75 interactions identified adjacent carbons at δ_c 31 and 24. Again HSQC identified the corresponding proton chemical shifts. The only un-assigned carbon δ_c 20.1 could be assigned by matter of elimination. Further support for the assignment can be observed though negative interaction; peaks that are not present. δ_c 70.9 does not see any interaction with protons bound to δ_c 23.6 as well as δ_c 83.2 does not see any interaction with protons bound to δ_c 20.1. This is expected as HMBC interaction over four bonds is rarely observed due to weak intensity over greater bond distances. Figure 29..

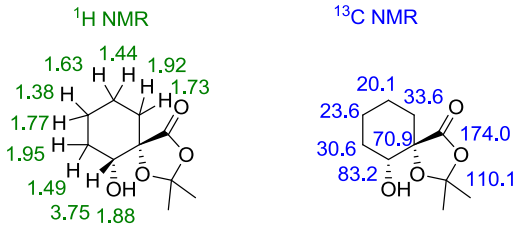


Figure 29: Complete assignment of compound 290 via interpretation of 2D-NMR spectra.

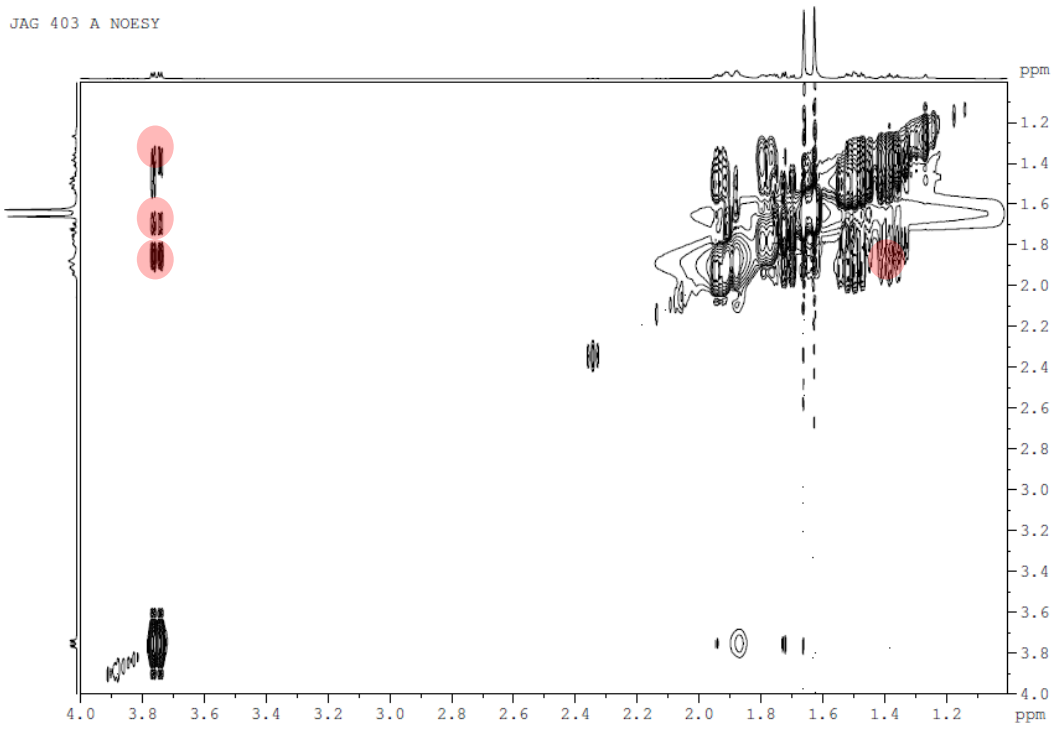


Figure 30: NOESY 2D-NMR Spectra of compound 290 indicating through space proton-proton interaction

Finally via analysis of NOESY spectrum could suggest the conformation of the cyclohexane ring. Axial protons at δ_H 3.75, 1.88, 1.73, 1.38 showed through space interactions. Figure 31.

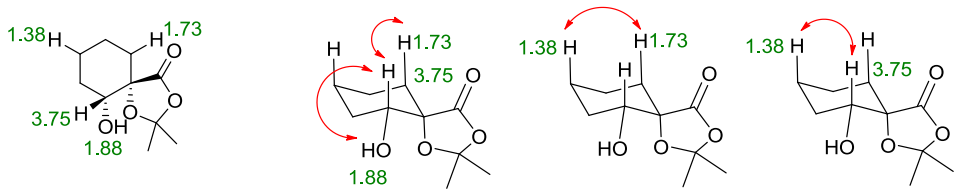


Figure 31: NOESY correlations which indicated conformational structure of compound 290.

In further support for the structure, the polarity of the compound, R_f = 0.50 (50% EtOAc-petrol), this is much more a-polar than any of the previous isolated carboxylic acids, suggesting an ester functionality rather than acid. Furthermore, analysis of the ketal resonance in the carbon spectra at δ_c 110 is in support of a five membered ring, structure **390**, rather than a possible six membered ring as shown in **391**. This is supported by literature studies;[106] five membered acetonides have characteristic quaternary carbon chemical resonances between 108 – 111 ppm, whereas six membered ketals have shifts between 97-101 ppm. Figure 32.

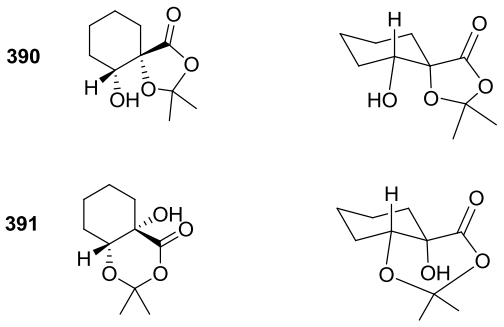
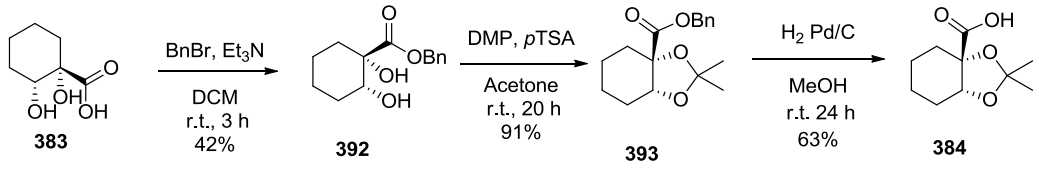


Figure 32: Five or Six membered acetonide?

To summarise, formation of acetonide protected acid **384**, via methyl esters, is possible via this route, although the basic hydrolysis step proves unreliable due to decomposition and rearrangement.

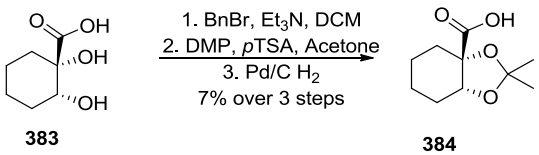
6.2.5 Formation via Benzyl Esters

We next investigated benzyl esters as their deprotection can be achieved without basic hydrolysis. Carboxylate alkylation of **383** was selective in formation of the ester **392** 33-42% and no benzyl ethers were observed. Acetonide protection gave benzyl ester **393** in a considerably improved 91% yield. In contrast to the methyl ester **388** the benzyl ester hydrogenolysis was successful, to give **384** in a 63% yield. Scheme 103.



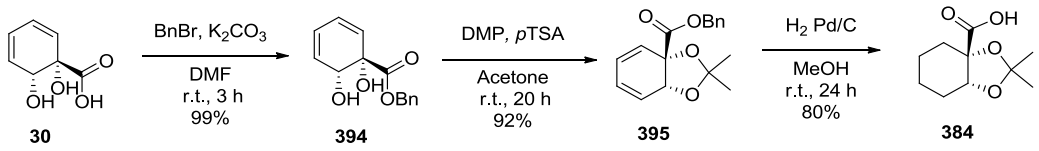
Scheme 103: Benzyl ester route to acid catalyst 384.

Telescoping the process resulted in an overall reduction in isolated yield. Scheme 104. This indicates the sensitive nature of the desired acetonide protected acid, as telescoping would lead to a build-up of impurities.



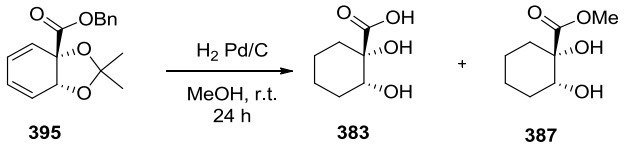
Scheme 104: Telescoped process.

The previous synthesis of the acetonide acid involved two hydrogenation steps, Scheme 103, one to reduce the alkenes in **30**, one to deprotect the benzyl ester **393**. Combining the hydrogenation steps to form the acetonide acid **384** in three steps from the MAO product was successful. Scheme 105. From the known benzyl ester **394**,[76] facile acetonide protection achieved **395** in a 92% yield and the optimised hydrogenation to remove both diene and ester **384** was achieved in 80% in the first instance.



Scheme 105: Combined hydrogenation steps.

However, the final hydrogenation step to form **384**, proved inconsistent; decomposition product diol acid **383**, methylester diol **387**, unidentifiable byproducts and significant loss of mass were observed on purification. This suggests autocatalytic deprotection. Scheme 106.

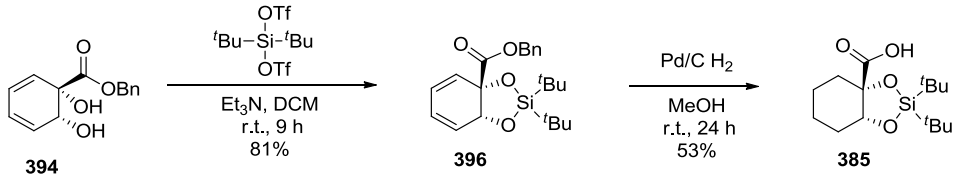


Scheme 106: Decomposition products observed.

Issues of decomposition upon purification were addressed by using a dry column chromatography method,[213,214] being able to isolate up to 80% of **384** from hydrogenation of **395**. At this stage we have a stabilised route through to the acetonide acid **384** in three steps from the product of MAO.

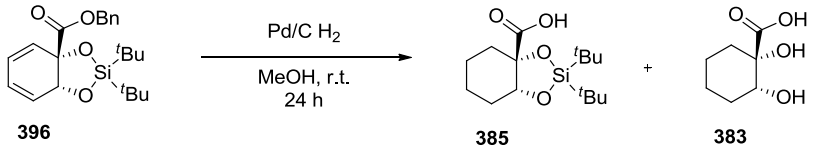
6.2.6 Silicon protection of esters.

With benzyl ester **394** in hand, we sought again to attempt silyl protection. Scheme 107. This was achieved easily in 75 – 81% yield. This was followed by facile reduction/deprotection to give **385** in 53% yield.



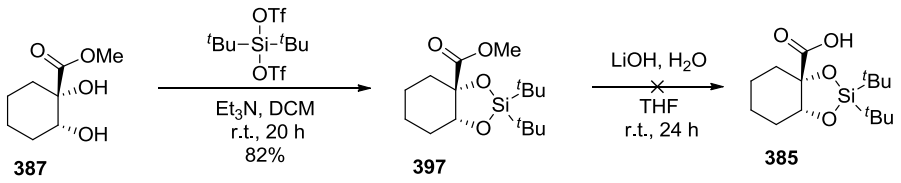
Scheme 107: Silyl protection of esters to form silyl acids.

However, again, disappointingly repetition of the final deprotection step, purification lead led to decomposition of the silyl acid **385** down to the diol acid **383**. Scheme 108. This again indicates the instability of this type of compounds with respect to both purification and autocatalytic deprotection.



Scheme 108: Decomposition of silyl acid on purification.

Starting with the methyl ester **387**, silicon protection was successful to form **397** with an 82% yield, however basic hydrolysis was not. Again this could be due to the acid sensitive nature of the product in the work up, which involves careful acidification of the basic hydrolysis mixture to neutral conditions. Scheme 109.

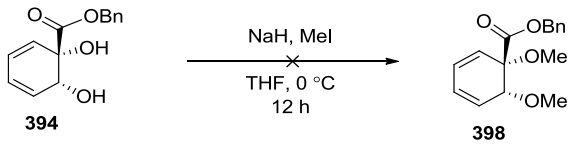


Scheme 109: Silyl protection of methyl ester

6.2.7 Methyl Ethers

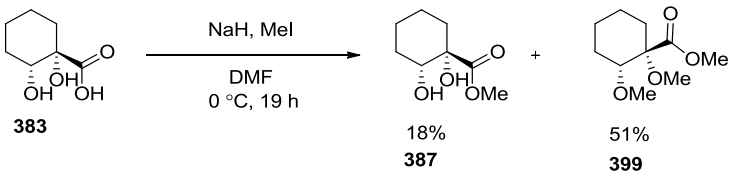
At this stage, it had been demonstrated how sensitive the most commonly applied hydroxyl protecting groups are to the presence of the acid side chain on the molecule. A hydroxyl derived functional group that was not acid or base sensitive was needed; methyl ethers were considered appropriate. [215]

Unsurprisingly attempted formation of **398** from diene benzyl ester **394** was unsuccessful, and shows that this type of diene *cis*-diol is sensitive to acidic and basic conditions and readily rearomatises. Scheme 110.



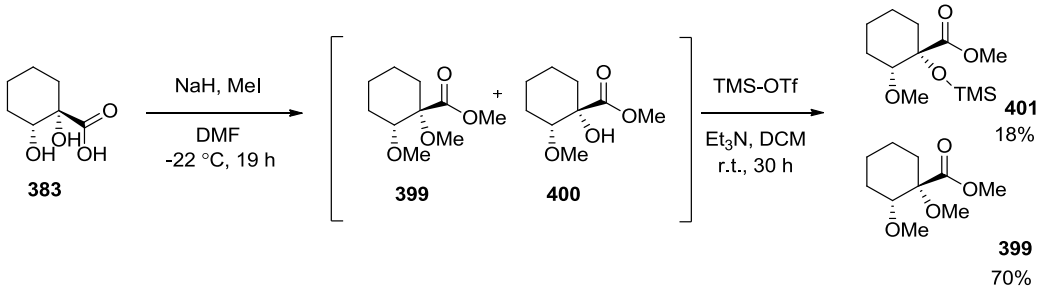
Scheme 110: Attempted methyl ether formation.

Diol acid **383** and 2 equivalents of methyl iodide, gave methyl ester **387** 18% and desired product, protected ether **399** 51 %, which could be separated. Scheme 111.



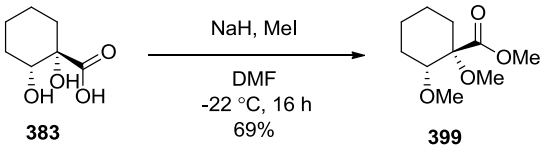
Scheme 111: Attempted methylation

Repeating the procedure with 3.4 equivalents of MeI, two inseparable esters were identified. Silicon protection of the mixture, **399** and **400**, facilitated separation to give silyl compound **401** 18% and di-ether **399** 70% over two steps. Scheme 112.



Scheme 112: bis(methyl ether) formation

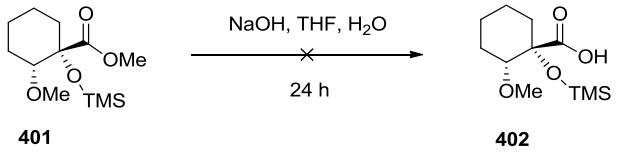
Upon optimisation and incorporating an excess of methyl iodide, 4 equivalents, the diether **399** was obtained, 69% as the sole product. Scheme 113.



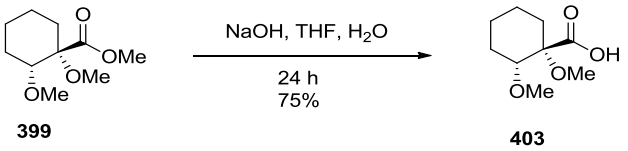
Scheme 113: Optimised methylether formation

In order to obtain the desired chiral acids, basic hydrolysis of the methyl esters was required. Unfortunately hydrolysis of these methyl esters proved inconsistent. Hydrolysis of silicon ether **401**, was unsuccessful and recovered small amounts of

starting material. Scheme 114. More success was obtained with the di methyl ether **399**, where 36-75% isolated yields were obtained. Scheme 115.



Scheme 114: methyl ester hydrolysis



Scheme 115: methyl ester hydrolysis

At this stage a reliable and reproducible route to di methyl ether acid **403**, in three steps form the product of MAO was in hand.

6.2.8 Other catalysts.

It is commonly known that to enhance stereoselectivity of a catalyst the two most important factors are steric bulk and electronic properties of the catalyst, as was shown by Miller and his carbamate – peptide interactions,[202] and Shi and his pyranose ketones.[184]

Thus synthesis of bicyclic acid catalysts was attempted in order to enhance any stereoselectivity observed. Following the Ley carbohydrate protection methodology[216,217] we sought to protect the diol functionality using 2,3-Butanedione and trimethyl orthoformate. Considering the double anomeric effect present in **405**, this would be expected to be the favoured diastereomer. Figure 33.

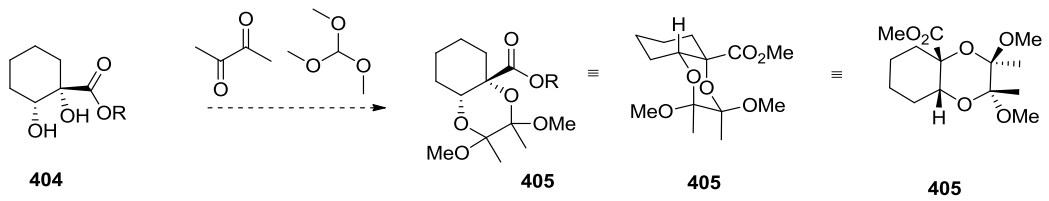
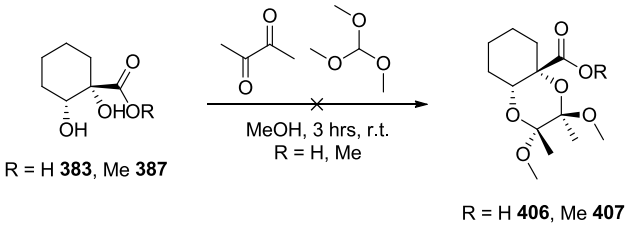


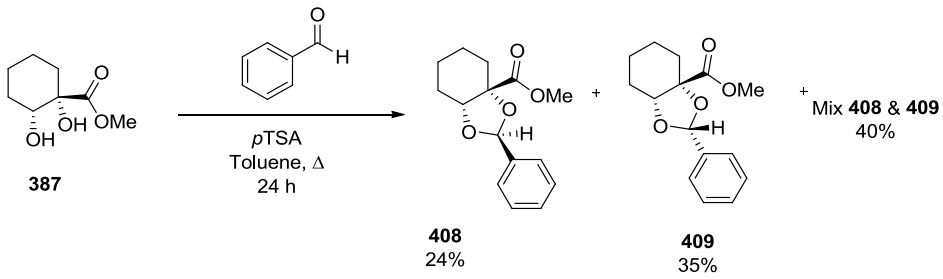
Figure 33: Expected product from ley protection.

Attempts on both the acid **383** and methyl ester **387** using methanol were unsuccessful. Very small amounts of product were identified when utilising a *p*TSA acid catalyst and CH_2Cl_2 as the solvent. The small mass isolated, complex NMR and the TLC showing multiple components with similar R_f, suggests different diastereoisomers had formed and would be difficult to isolate and purify. This was not pursued.



Scheme 116: Ley protection.

In a different approach with methylester **387**, diastereomer formation with benzaldehyde was investigated. It was speculated that different diastereoisomers may result in different stereoselectivity. Attempts using CH_2Cl_2 at room temperature gave recovered starting material. Utilising THF at reflux resulted in THF being incorporated into the products. Success was finally obtained using toluene as the solvent and refluxing for 24 h. Scheme 117.



Scheme 117: Benzyaldehyde acetal protection

Diastereoisomers were separated by column chromatography; unfortunately they could not be separated completely and a 1:1 mix of **408** and **409** was obtained in a 40% yield, in addition to 24% of **408** and 35% of **409**.

Identification of the diastereoisomers **408** and **409** could be achieved using NOESY NMR spectroscopy. Additionally the 3D modelling indicates that the lower yield in

408 could be due to steric clash of the aromatic ring with the carbonyl group. Figure 34 and Figure 35.

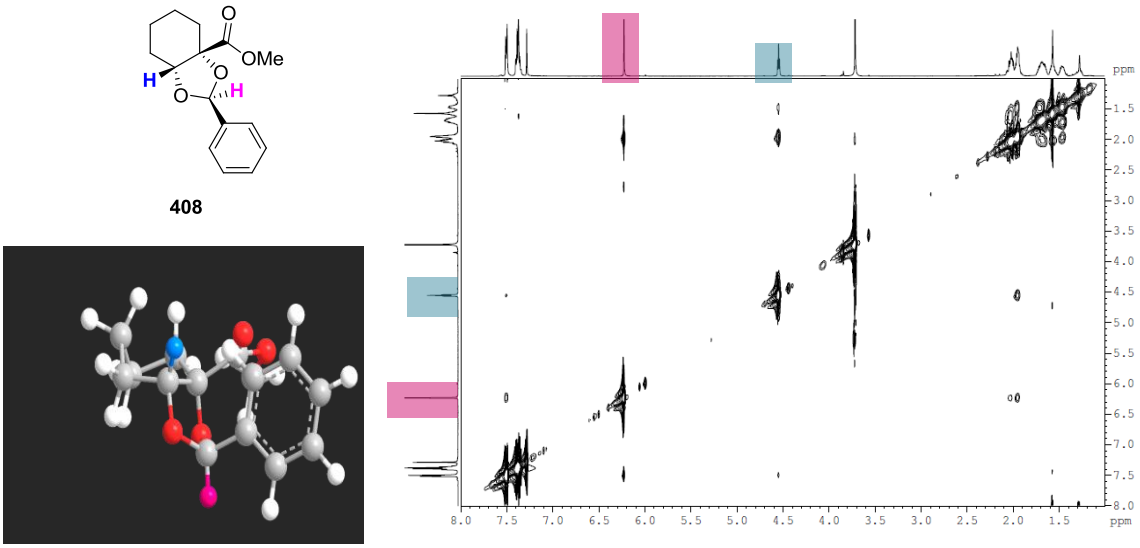


Figure 34: NOESY NMR spectroscopy of 408, to determine diastereoisomer.

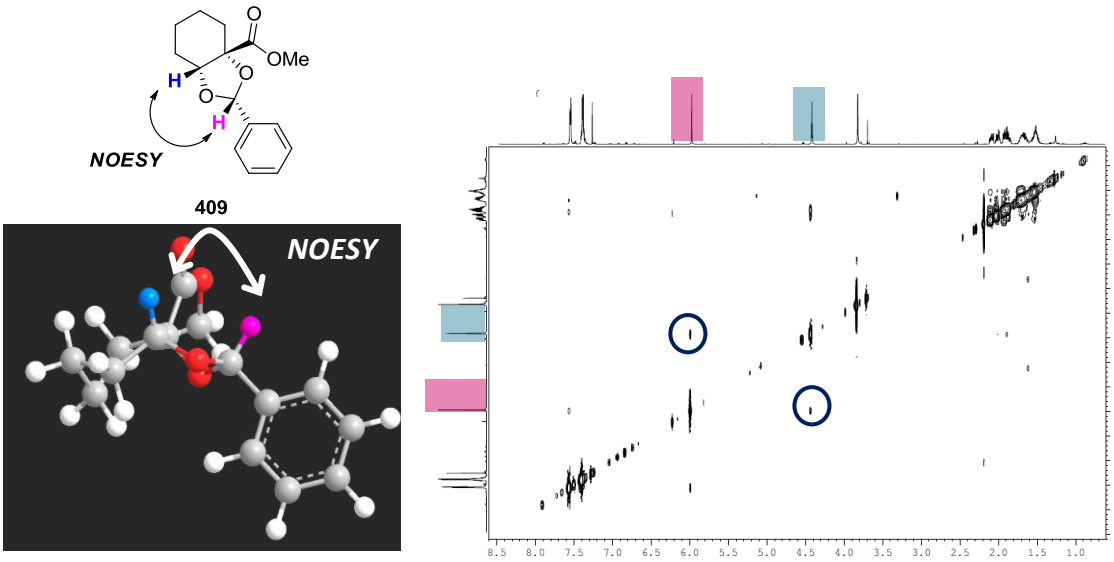
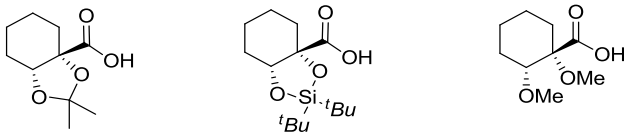


Figure 35: NOESY NMR spectroscopy of 409, to determine diasetereoisomer.

6.3 Conclusions – Catalyst Synthesis

At this stage several different routes have been scoped for the viability of synthesising a range of chiral acid catalysts derived from the *ipso, otho cis*-diol MAO product of benzoic acid.

Three chiral acids **384**, **385** and **403** have been synthesised. Scheme 118 In the next section these chiral acids have been evaluated for their catalytic activity in asymmetric epoxidation reactions.



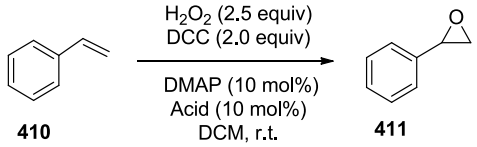
384 **385** **403**

Scheme 118: Chiral acids synthesised

6.4 Results and Discussion: Catalyst Testing

6.4.1 Initial Catalyst testing

Using Miller et al. [201] as a starting point for reaction optimisation, styrene **410** was chosen as a substrate, *N,N'*-Dicyclohexylcarbodiimide (DCC) was chosen as the available carbodiimide coupling agent and benzoic acid as the achiral acid catalyst for comparison to the synthesised chiral acids. Scheme 119.



Scheme 119: Preliminary conditions used for catalyst testing.

The subsequent reactions evaluated at many variables to predominantly achieve high conversions and investigate the roles of each of the components to gain greater insight into the reaction. Results of conversions and specific reaction conditions are graphically shown below. Table 4.Graph 1.

Rxn	H_2O_2	DCC	DAMP	Acid	Other	Conversion
R1	✓	✓	✓	×	No Acid 0.87 M	59%
R2	✓	✓	✓	✓	Dilute Conditions 0.18 M	18%
R3	✓	×	×	×	Just H_2O_2	0%
R4	✓	✓	×	×	Just H_2O_2 + DCC	21%
R5	✓	✓	✓	✓	Alkene added last	48%
R6	✓	✓	✓	✓	Chiral Acid **384** Alkene added last	12%
R7	✓	✓	✓	✓	DCC last	51%
R8	✓	✓	✓	✓	Alkene added after 1 h	19%
R9	✓	✓	✓	✓	-22°C to r.t. DCC last	44%
R10	✓	✓	✓	✓	Exact replicate R9	63%
R11	✓	✓	✓	✓	Chiral Acid **385**, DCC added last	11%

Table 4: Initial Reaction optimisation conditions

An initial reaction **R1** 0.87 M in the absence of benzoic acid gave a conversion of 59%, this suggests the benzoic acid is not essential for the reaction to take place, and that a background reaction is significant. A dilute reaction in the presence of benzoic acid **R2** under dilute conditions for 20 h at 0.18 M resulted in a disappointing conversion of 18%. (N.B. all subsequent reactions were carried out at 0.87 M for consistency and comparability of results.)

Further investigations into the specific roles of each of the components, **R3** showed that hydrogen peroxide alone was insufficient, and only in the presence of DCC **R4** would the reaction proceed, albeit with a lower conversion, 21%. This result is of interest as the conversion is higher than that for the dilute reaction **R1**, suggesting the concentration plays a key role. The presence of DMAP **R5** again improved conversions to 48%.

Initial reactions using a chiral acetonide catalyst **384** under these standard conditions **R6**, at 0.87 M, and employing addition of the styrene after an hour, in an attempt to allow the peracid to form *in situ*, progressed with a disappointing 12% conversion.

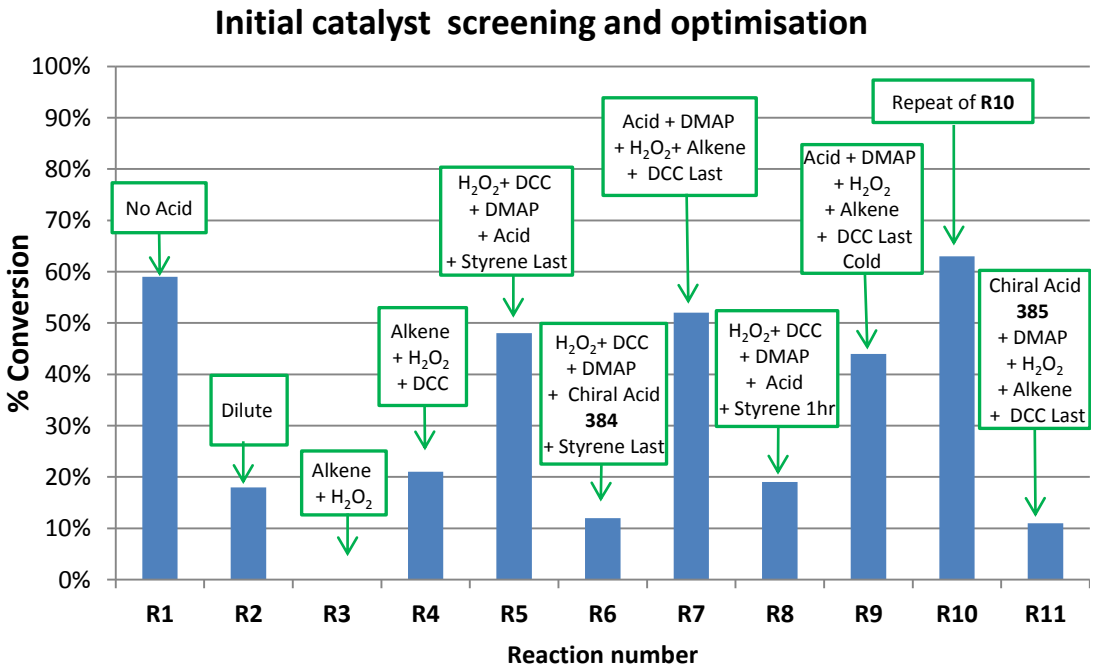
Following the Miller precedent, which added the diimide last, 'added to start the reaction', in reaction **R7** DCC was added last in presence of benzoic acid gave a 51% conversion. Investigating further the order of addition, **R8** involved no acid and styrene addition after an hour gave 19% conversion.

Results to briefly scope the effect of temperature, in reactions **R9** and **R10** components were added at -22 °C and allowed to warm to room temperature slowly over the course of the reaction. **R9** added DCC last and gave a 44% conversion; a repeat of this **R10** to observe reproducibility of results gave a 63% which suggests poor reproducibility. Disappointingly **R11** using chiral acid **385**, achieved a meagre 11% conversion.

Considering the length of reaction, **R1** and **R2** were left for 20 h, **R3** to **R8** were left for 90 h and **R9** to **R11** for 60 h. Firstly considering this length, conversions are low

and unimpressive, the significant difference in time does not result in a significant difference in conversion. It is worth noting Miller also reported some lengthy reaction times over several days.

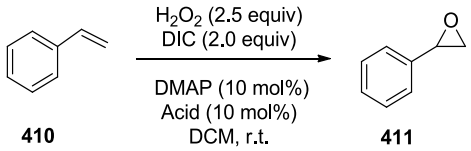
To summarise the above results, it is obvious there is little reproducibility and consistency between comparable reactions. Notably the use of DCC proved problematic in the aqueous work up and extraction, the DCC urea derived byproduct precipitated and caused poor phase separation. Future reaction optimisations will consider other carbodiimides such as *N,N'*-Diisopropylcarbodiimide (DIC) and *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI).



Graph 1: Initial catalyst screening and optimisation

6.4.2 Reaction Optimisation Using DIC

Again using Miller[201] as a starting point for reaction optimisation, *N,N'*-Diisopropylcarbodiimide (DIC) was chosen as the available carbodiimide and benzoic acid as the achiral alternative for comparison to the latter synthesised chiral acids. Scheme 120. Considering the variety in reaction conditions investigated in the previous section, a more systematic approach was taken, results shown in Table 5 and Graph 2.



Scheme 120: Starting point for reaction optimisation using DIC.

Rxn	Investigation	Outcome	Max conversion
R12	Solvent Screen	Acetone	19%
R13	Use of a carousel	Acetonitrile – improved mixing	32%
R14	Order of addition	Very little difference	26%
R15	Amount of DMAP	20 mol% beneficial	36%
R16	Concentration H_2O_2	50% H_2O_2 had no effect	27%
R17	Concentration of reaction	4.0 M improved conversion	44%
R18	Amount of H_2O_2	1.0 mL 12 equiv.	77%
R19	Amount of DIC	4 equiv., 2 used for solubility	83%
R20	Solvent screen	Acetonitrile	66%
R21	EDCI	Water soluble diimide	2%
R22	Chiral acids **384** and **385**	Under optimised conditions	72%

Table 5: Overview of reaction optimisation investigation and outcomes.

Initial solvent screen of the reaction **R12** and **R13** scoped a variety of different solvents; Acetonitrile was the best performing solvent with 32% conversion, followed by MeTHF 23%, CH_2Cl_2 21% and 2-butanone 19%. As suspected polar aprotic solvents are beneficial for the reaction, and CH_3CN being water miscible promotes the reaction.

Improved mixing and use of a carousel was implemented from **R12** to **R13**. The benefits are shown noting **R12.1** and **R13.1** both use CH_2Cl_2, conversion of 13% to 21% respectively indicates the importance of uniformed and good mixing in a biphasic reaction. Use of a phase transfer catalyst, tetrabutylammoniumbromide (TBAB), ceased the reaction and was not further investigated. **R12.2**

R14 investigated order of addition of the reagents, using MeCN as the optimal solvent. In his work Miller presents two methods:

General Procedure a: Acid + DMAP + Solvent + Alkene + H_2O_2 + DIC

General Procedure b: Alkene + Acid + Solvent+ H_2O_2 + DIC + DMAP

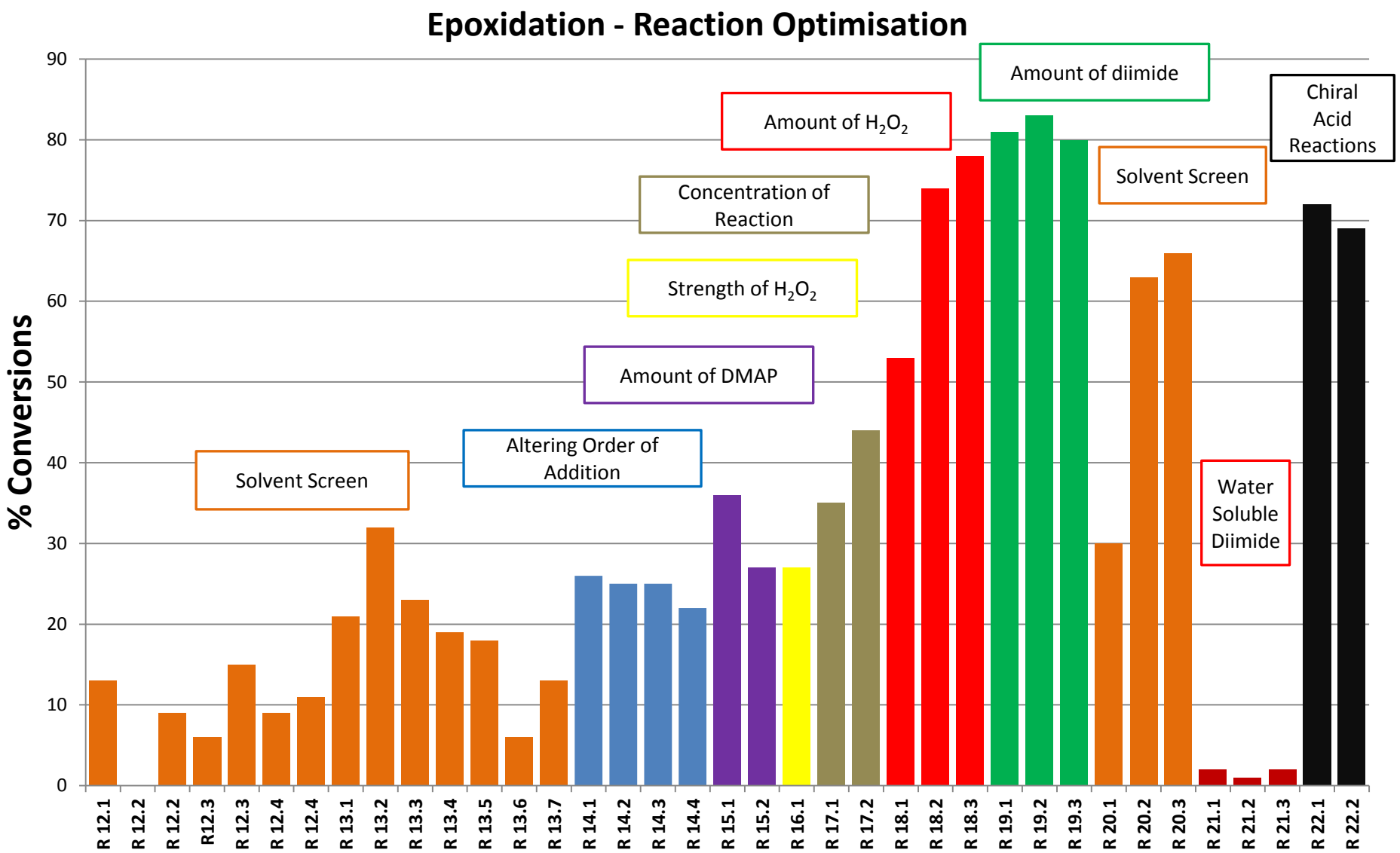
As it is obvious there are two possible pathways for epoxide formation, one using the acid catalyst, one not, [218] it would seem important that the active oxidant is the chiral peracid and not the DIC-peroxide complex. In order to promote peracid formation the procedure below was employed. The length of stirring was varied 0 mins, 5 mins, 1 h.

Procedure c: Acid + DIC + DMAP + Solvent (Stir), then H_2O_2 (Stir), then Alkene

Results indicated very little difference in conversions, 22-26%, which indicates that order of addition is not of primary importance.

R15 investigated increasing the amount of DMAP, as this should improve the rate of formation of the peracid over the DIC-peroxide species.[201] Results showed that 0.2 equiv improved conversion to 36% however 0.4 equiv reduced conversion to 27%. Possibly due to competing reactions and formation of byproducts are indicated by the Miller report. [201]

The next set of experiments **R16** and **R17** evaluated concentration of the reaction and the peroxide concentration and equivalents. Again using the standard conditions and acetonitrile; the use of concentrated, 50% H_2O_2, 2.5 equiv **R16** showed slight improvement to 27%. Varying the concentration of the reaction, **R17.1** from 0.8 M to 1.0 M in MeCN improved conversion to 35%, further concentration **R17.2** to 4.0 M further improved conversion to 44%.



Graph 2: Reaction Optimisation using DIC

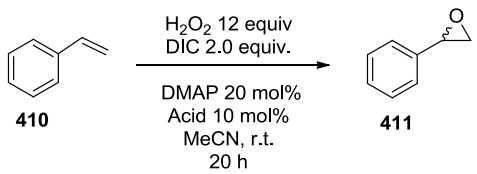
R18 kept the concentration constant at 0.8 M while varying the amount of H_2O_2 added, from 0.4 – 1.0 mL, showed a dramatic increase in conversions, as 1 ml equates to 12 equivalents of oxidant, a 78% conversion was observed as the best achieved so far.

Finally **R19** investigated how equivalents of DIC affected conversions; as expected increasing the amount of diimide improves conversion, however not to the extent that varying quantity of the oxidant did. Conversion ranged between 80% to 83%.

Finally a solvent screen **R20** was performed for a second time to confirm that MeCN was the optimal solvent. Solvents chosen were previously tested CH_2Cl_2, MeTHF and Acetone, as these were the best performing solvents from previous screens. Conversions for these other solvents dropped dramatically which indicated unambiguously that MeCN is the solvent of choice.

A drawback from all of the work carried out above is the presence of an insoluble urea byproduct, this can be filtered out however even after chromatography it sometime may persist. Use of a water soluble diimide EDCI[219] was investigated as would be removed in aqueous work up. However reactions using EDCI did not proceed. No conversions were observed.

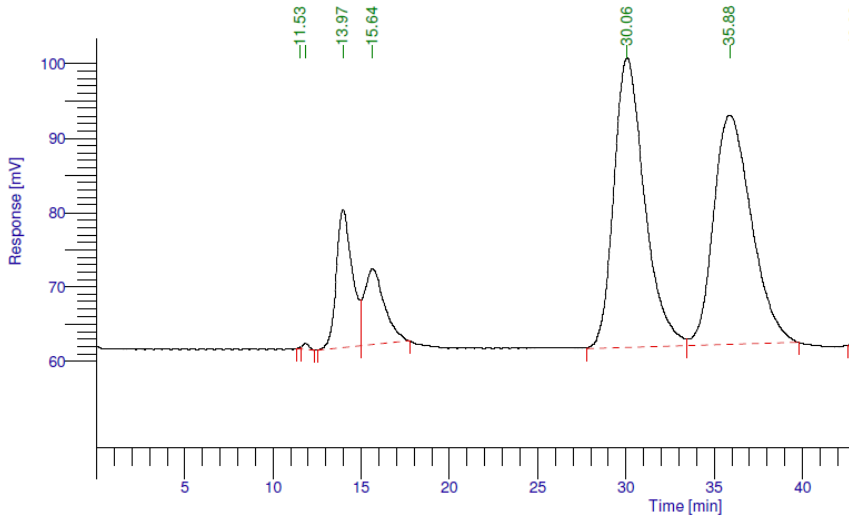
To summarise, conditions have been optimised to greatly improve the conversion of the reaction over the 20 h given time frame. Scheme 121.



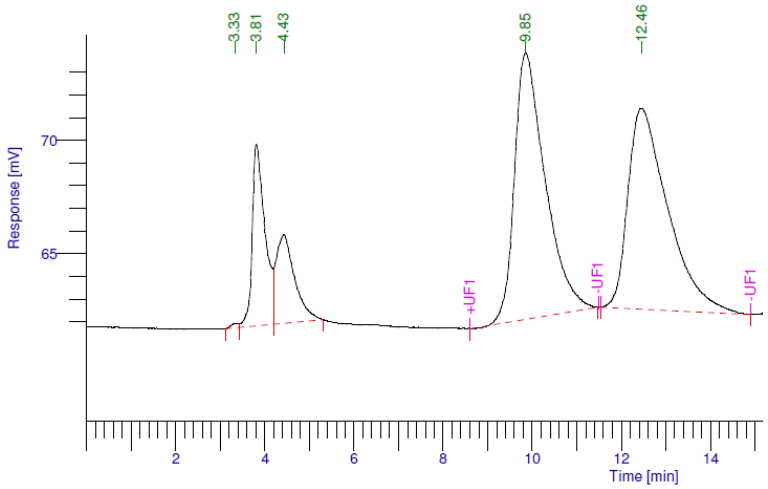
Scheme 121: Optimised conditions.

6.4.3 HPLC Methods

Chiral HPLC methods were developed for styrene oxide **411** as the chosen substrate. The first: Chiralpak AS. 0.2 mlmin^{-1}. 0.6% IPA/Hexane, 254nm. This gave good baseline separation and peaks of equal integration at t_1 = 30 mins and t_2 = 35 mins. Graph 3. The second shortened the method significantly: Chiralpak AS. 0.8 mlmin^{-1}. 0.2% IPA/Hexane, 254nm. This gave good baseline separation and peaks of equal integration at t_1 = 9.9 mins and t_2 = 12.4 mins. Graph 4.



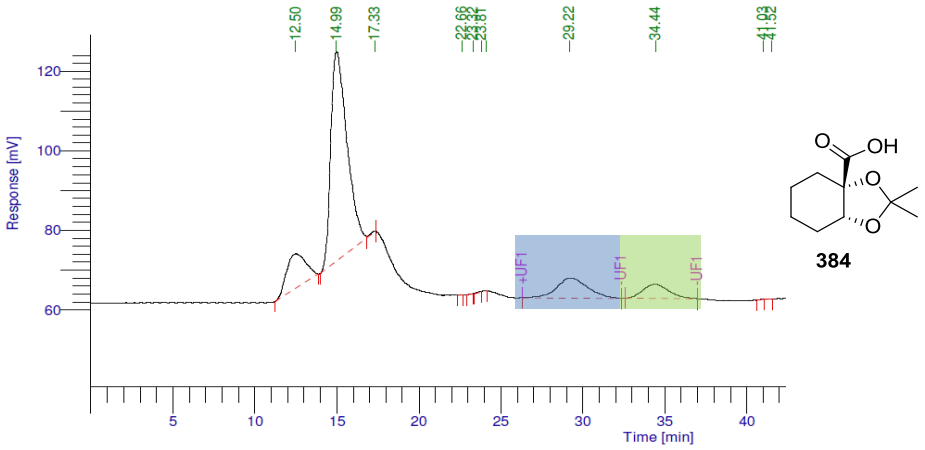
Graph 3: Method 1. Styrne oxide, racemic, HPLC separation. Chiralpak AS. 0.2 mlmin^{-1}. 0.6% IPA/Hexane, 254nm. t_1 = 30 mins and t_2 = 35 mins



Graph 4: Method 2. Styrene oxide, racemic, HPLC separation. Chiralpak AS. 0.8 mlmin^{-1}. 0.2% IPA/Hexane, 254nm. t_1 = 9.9 mins and t_2 = 12.4 mins

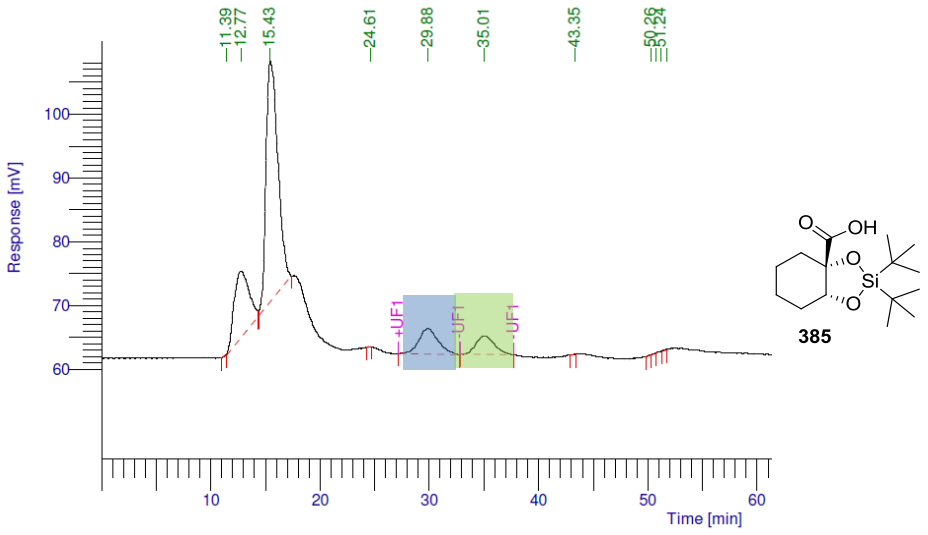
6.4.4 Chiral Acid Epoxidations HPLC results – unoptimised conditions

During the reaction optimisation process some chiral acids were evaluated and tested for their enantioselectivity, albeit under un-optimised reaction conditions. Scheme 119 & Graph 1. Using the chiral acetonide acid **384** in reaction **R6**, a 12% conversion and a 25% *ee* was calculated via HPLC method 1. Graph 5.



Graph 5: R6 using chiral acetonide acid 384 HPLC result. HPLC method 1.

Reaction using the silicon protected acid **385** in reaction **R11** gave a 11% conversion and a calculated selectivity of 6% *ee,* again using HPLC method 1. Graph 6.



Graph 6: R11 using chiral silicon acid 385 HPLC result. HPLC Method 1.

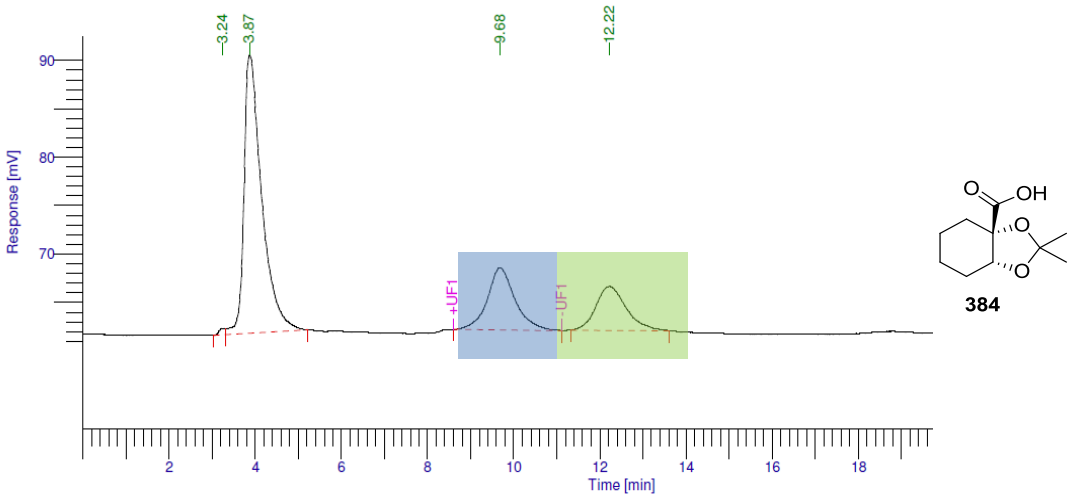
At this stage of reaction screening, it is worth emphasizing that these are un-optimised conditions, using an unfunctionalised substrate and a fairly minimally functionalised catalyst. Although the reactions are low yielding, the selectivity

observed is not zero. It is also worth noting that the HPLC quality is mediocre, this is due to samples being unpurified, residual styrene can be removed under reduced pressure, and most of the urea byproduct can be filtered off, however some still persists, often resulting in poor quality chromatograms. Nevertheless, at this early stage of catalyst screening, these resulting presented an excellent starting point for catalyst development an encouraged the work to continue.

6.4.5 Chiral Acid Epoxidations HPLC results – optimised conditions

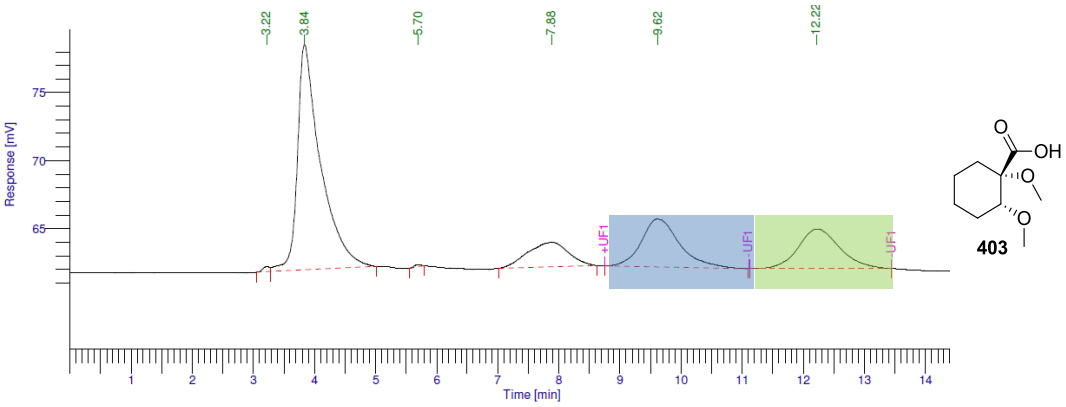
After optimising the reaction conditions. Scheme 121 & Graph 2. Some more chiral acids were tested under the optimised reaction conditions and analysed using HPLC method 2.

Repeating the chiral acetonide **384** under the optimised reaction conditions **R22.1** resulting in an increased conversion to 72%, however as a penalty selectivity reduced to 14% *ee*. Graph 7.



Graph 7: R22 chiral acetonide acid under optimised conditions. HPLC method 2.

Using the di-methyl ether acid **384** under the optimised conditions **R22.2** again gave a sufficient conversion of 69%, however disappointingly a selectivity of only 4% *ee,* which could be attributed to error or variation in either integration, base line effects or sample preparation. Graph 8.

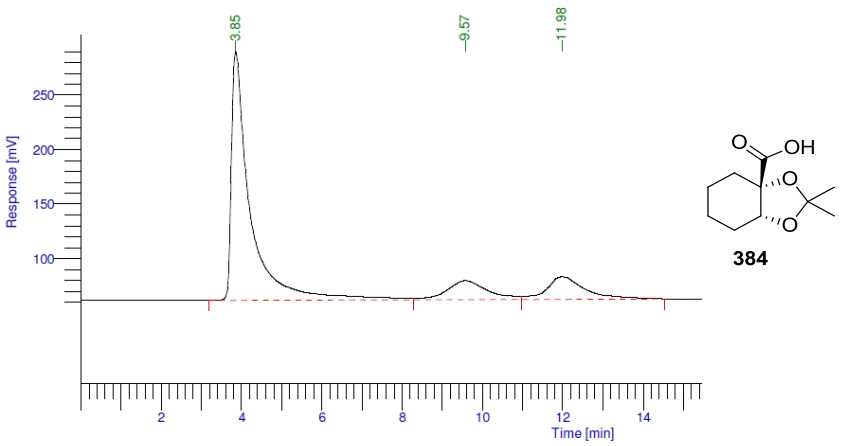


Graph 8: R19.2 Chiral di-methyl ether 403 under optimised conditions. HPLC method 2.

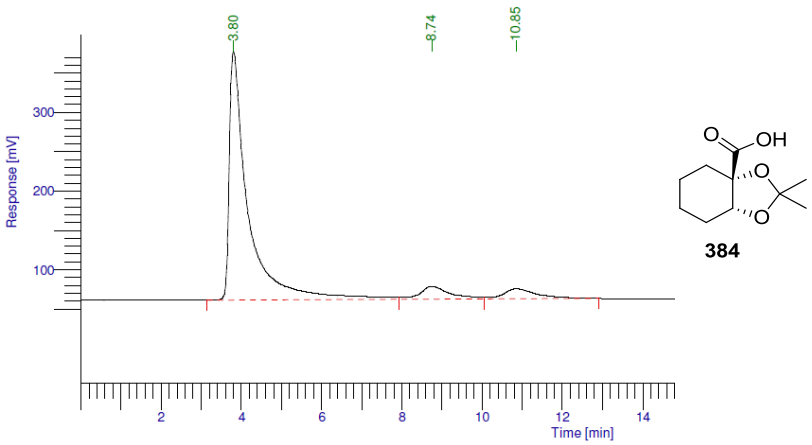
At this stage, chiral HPLC's are of singular reactions, to ensure validity of results it is essential that they are repeated. **R22.1** was chosen to be replicated as showed the best enantioselectivities. Results are shown below. Table 6, Graph 9, Graph 10.

Reaction	Conv.	% *ee*
R 22.1	72%	14%
R 23.1	80%	6% A
R 23.2	70%	6% B

Table 6: Repeating chiral acid reactions



Graph 9: R23.1 repeat of R22.1 HPLC Method 2.



Graph 10: R23.2 repeat of R22.1. HPLC Method2.

Unfortunately these repeated chiral catalysts runs, not only show a reduction in the selectivity of 6% *ee*, which is small enough to be considered error, but additionally inversion of the selectivity was observed between runs.

6.4.6 Summary HPLC results

These results, despite optimisation, have shown that an increase in conversion has not enhanced the selectivity. It is worth considering whether the catalyst is playing a vital role. Under the optimised conditions reaction with benzoic acid gave a 79% conversion, and without benzoic acid gave 74%. This suggests the acid catalysed process has in effect has become the background reaction, and the known background reaction of di-imide and hydrogen peroxide[218,220] to form the complex **412** is actually performing the majority of the epoxidations. Figure 36.

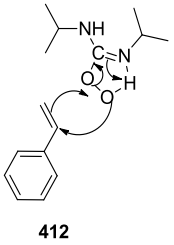


Figure 36: Epoxidation of styrene via di-imide and peroxide complex.

To summarise the above chiral HPLC results – it has been shown that some selectivity has been observed, maximum 25% *ee*, other results have been much less, and even racemic.

The optimisation of the reaction conditions has led to the chiral catalyst playing little part in the reaction; this needs to be addressed.

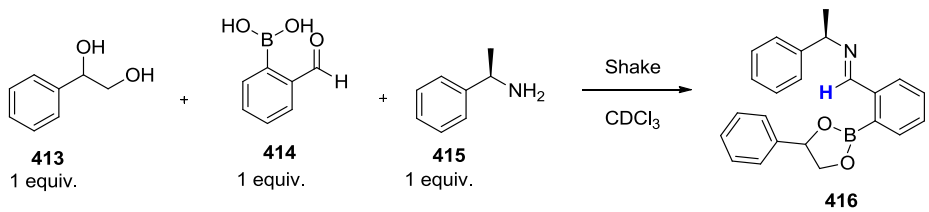
It is also worth noting the difficulty in obtaining good quality HPLC for styrene oxide, despite through optimisation and trials of many different columns, conditions and methods, DIC urea byproduct in samples leads to poor quality traces.

From all the above and from the start, it has been aware that the epoxidaiton proceeds in the absence of acid, and since been shown that the background reaction, via intermediate **412**, is now very much in the foreground. In an attempt to address this both varying urea source and coupling agent will be considered.

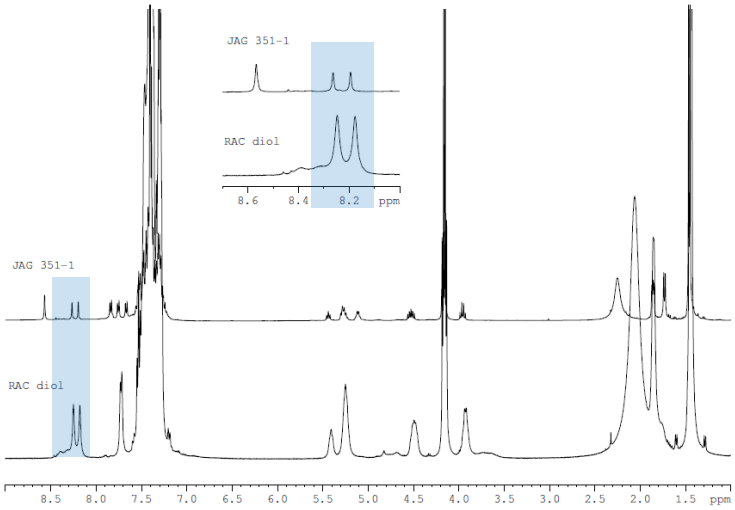
6.4.7 Different coupling agents

DIC, DCC are all common peptide coupling agents. Other coupling agents were identified and tested. Under the optimised reaction conditions EDCI and HATU, both on their own and with the addition of HOBt activating agents gave no reaction. The use of T3P® (Propane Phosphonic Acid Anhydride) did not give the desired epoxide, instead ring-opened to form the corresponding diol **413**. [219]

The diol was analysed for its enantioselectivity by known methodology. [221] Formation of an imine **416** with addition of boronic acid **414** and chiral amine **415** was followed by NMR spectroscopy. Analysis and integration of the diastereotopic protons of the imine, showed a racemic mixture had been formed and hence no enantioselectivity was induced in the epoxidation.



Scheme 122: Formation of chiral imine to calculate enantioselectivity.

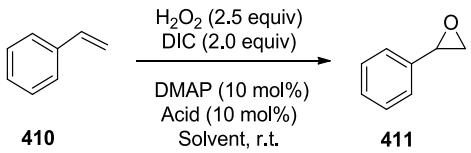


Graph 11: Overlaid NMR spectra of imine diastereoisomers.

6.4.8 Different urea source.

Initially investigations used aqueous H_2O_2, however this is not the only possible oxidant and others are used in industry. Most commonly used is urea hydrogen peroxide, due to cost, ease of handling and safety.

Under the optimised conditions, hydrogen peroxide urea gave a 13% conversion, which is a reduction to the 80% observed using the aqueous peroxide solutions. This reduction in conversion could be attributed to a solubility issue, to enable a direct comparison a solvent screen using urea hydrogen peroxide was carried out under un-optimised conditions, to enable a direct comparison to previous solvent screen results. Scheme 100 and Table 7.



Scheme 123: Conditions for urea H_2O_2 solvent screen.

Solvent	Urea H_2O_2	Aqueous H_2O_2
CH_2Cl_2	<1%	21%
Me-THF	0%	23%
Acetone	14%	15%
Butanone	<1%	19%
MeCN	9%	32%

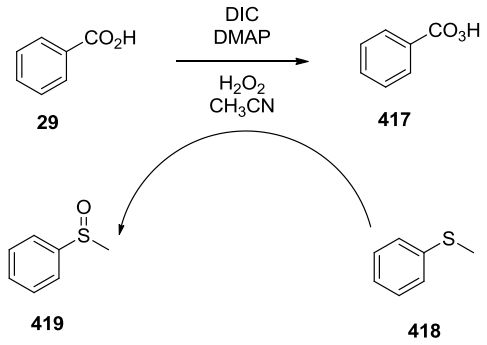
Table 7: Solvent Screen Urea Hydrogen peroxide compared to aqueous peroxide.

These results indicate that urea hydrogen peroxide is not a good candidate, as the aqueous peroxide performs better in all cases.

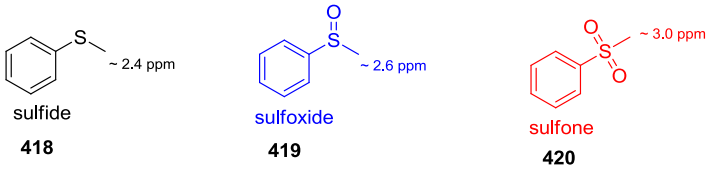
6.4.9 Is the active catalyst actually being formed?

All the above results suggest the known background reaction is significant. For absolute conformation, isolated and purified chiral peracid catalyst would need to be synthesised to evaluate its ability to directly epoxidise alkenes, rather than being generated in *situ*. However this is not possible due to the difficulty and risk associated in isolating potentially explosive peracid material. Additionally peracid synthesis often requires a strong acid, which is not viable for our acetonide acids, as would result in deprotection. Alternative analysis needs to be performed.

It is known within the literature that oxidation of organic sulfides to sulfoxide occurs rapidly with peracids and proceeds very slowly with hydrogen peroxide. Methodology has been developed using GC to determine the amount of active peracid in the presence of an excess of hydrogen peroxide. [222] The same theory can be transferred to develop NMR spectroscopic method. Scheme 124. If the peracid is formed *in situ*, thioanisole **418** will be readily oxidized to methyl phenyl sulfoxide **419** which can be analysed via NMR spectroscopy, as the chemical shifts of the methyl protons are distinctive from one another. Scheme 125. Results & NMR spectra shown below Table 3.



Scheme 124: Reaction Scheme for testing prescence of peracid formation.



Scheme 125: Approximate chemical shifts of thianisole and corresponding sulfoxide and sulfone.

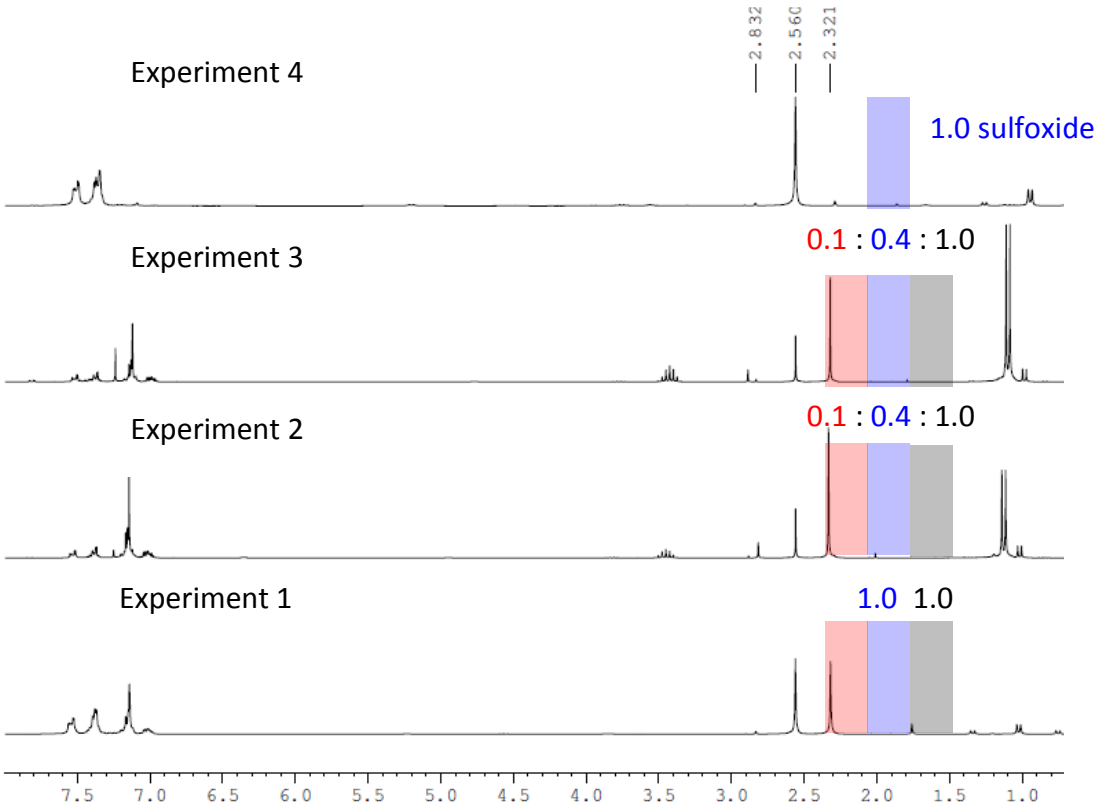


Figure 37: NMR spectra of reactions to determine presence of active peracid catalys.

Experiment number	Conditions	Sulfide 418	Sulfoxide 419	Sulfone 420
			relative ratios	
1	Benzoic acid 15 min	1.0	1.0	0
2	Chiral Acid **384** 1 h	1.0	0.38	0.13
3	No Acid 1hr	1.0	0.38	0.13
4	Benzoic Acid 1hr	0	1.0	0

Table 8: **1)** Benzoic acid (94 mg, 0.78 mmol, 1 equiv), DIC (0.24 mL, 1.54 mmol, 2 equiv), DMAP (19 mg, 0.16 mmol, 10 mol%) H_2O_2 (35 wt%, 0.79 mL, 12 equiv), thioanisole (484 mg, 3.9mmol, 5 equiv) MeCN (0.8 mL). Stirred r.t., 15 mins. Workup, add ice (5 mL), add $NaHCO_{3(aq)}$ extract $CHCl_3$ (3 × 10 mL), dry $MgSO_4$ concentrate under reduced pressure. **2)** Chiral acid **384** (68 mg, 0.34 mmol, 1 equiv), DIC (0.1 mL, 0.68 mmol, 2 equiv), DMAP (8 mg, 0.06 mmol, 10 mol%) H_2O_2 (35 wt%, 0.35 mL, 12 equiv), thioanisole (217 mg, 1.75mmol, 5 equiv) MeCN (0.35 mL). Stirred r.t., 60mins. Standard workup. **3)** DIC (0.1 mL, 0.68 mmol, 2 equiv), DMAP (8 mg, 0.06 mmol, 10 mol%) H_2O_2 (35 wt%, 0.35 mL, 12 equiv), thioanisole (217 mg, 1.75mmol, 5 equiv) MeCN (0.35 mL). Stirred r.t., 60mins. Standard workup. **4)** Benzoic acid (94 mg, 0.78 mmol, 1 equiv), DIC (0.24 mL, 1.54 mmol, 2 equiv), DMAP (19 mg, 0.16 mmol, 10 mol%) H_2O_2 (35 wt%, 0.79 mL, 12 equiv), thioanisole (484mg, 3.9mmol, 5 equiv) MeCN (0.8 mL). Stirred r.t., 15mins. Standard workup.

Experiment 1 indicated that, under the reaction conditions, benzoic acid was converted to perbenzoic acid resulting in 50% conversion of thioanisole to the sulfoxide in 15 mins.

Experiment 2 utilised the synthesised chiral acetonide acid **384**, under the same conditions as experiment 1 but instead over an extended period of 1 h, as we expect the catalyst could be less active. These results indicated a reduction in oxidative conversions, suggesting the chiral peracid is a poorer oxidative species.

Experiment 3 utilised the same reaction conditions as experiment 2, over 1 h, containing no acid species. This reaction was performed to observe the background oxidation via H_2O_2. With almost identical conversion to experiment 2, it suggests the only conversion observed in experiment 2 is due to oxidation via H_2O_2, and suggest the chiral peracid isn't being formed.

Experiment 4 was carried out to complete this series of investigations. Benzoic acid was utilised under the same conditions as experiment 2 & 3 for direct comparison over 1 h reaction time. Complete conversion to the sulfide was observed. This

suggests under these conditions benzoic acid is able to form the perbenzoic acid. Whereas in comparisioon under these conditions the chiral acid **384** isn't able to form the chiral peracid.

6.5 Conclusions

This final sulfide oxidation experiment, along with the unselectively and low conversions observed throughout the catalyst epoxidations optimisation process suggest that the chiral peracid isn't being formed under these reaction conditions, and hence why we see very little, if no selectivity.

It has been considered that this work will not be pursued further.

Despite this this section shows a range of synthetic procedure through to novel chiral acids – future work would hope to find application of these, or use as synthons towards subsequent organic targets.

7 Chapter 7: Shi Catalyst Analogue

As we have seen in the literature introduction to epoxidations Shi developed a range of catalysts of general type **344.** The aim of this work is to synthesise a Shi catalyst analogue **421** derived from the MAO product **30**. Notably similarities include the α-quaternary carbon. Differences include the lack of the endo cyclic oxygen and peripheral substituents around the cyclohexane ring.

Many similar carbocyclic ketones have also been shown to be active epoxidation catalysts, as seen in the previous epoxidations literature section.

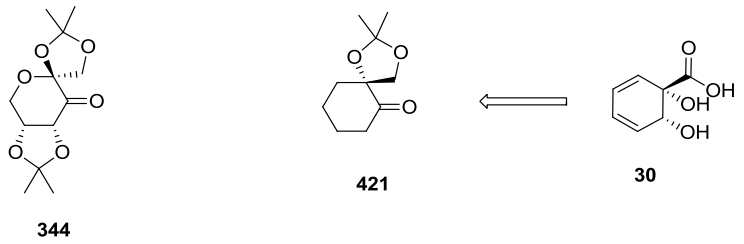
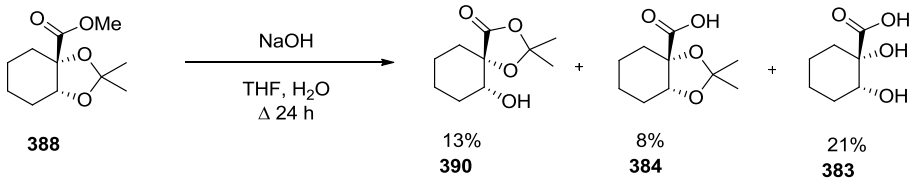


Figure 38: Shi Catalyst and proposed MAO derived catalyst

7.1 Shi Like Catalysts – Catalyst #1

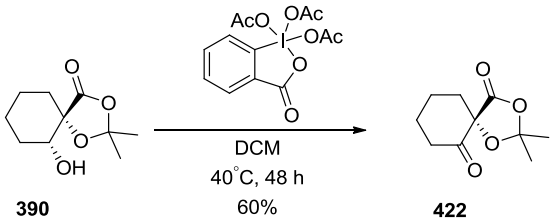
Within the previous chapter, in search for an asymmetric peracid epoxidation catalyst, compound **390** was isolated and fully characterised as a byproduct from the basic hydrolysis of methyl ester **388**. Scheme 126. With a quaternary centre α to the alcohol, and the acetonide protected side chain, there are obvious structural similarities to the Shi catalyst **344**.



Scheme 126: Shi like by product identified via basic hydrolysis of 388.

With **390** isolated and purified, oxidation to form the ketone, and direct Shi analogue **422** was evaluated. Scheme 127. Mild oxidative conditions were considered as deprotection or rearrangement of the acetonide was possible, as we have seen with compounds in the previous chapter.

Use of pyridinium dichromate (PDC) was unsuccessful, recovering starting material. Dess Martin periodinane gave sufficient yield of 60% with the remaining isolated mass being recovered starting material.

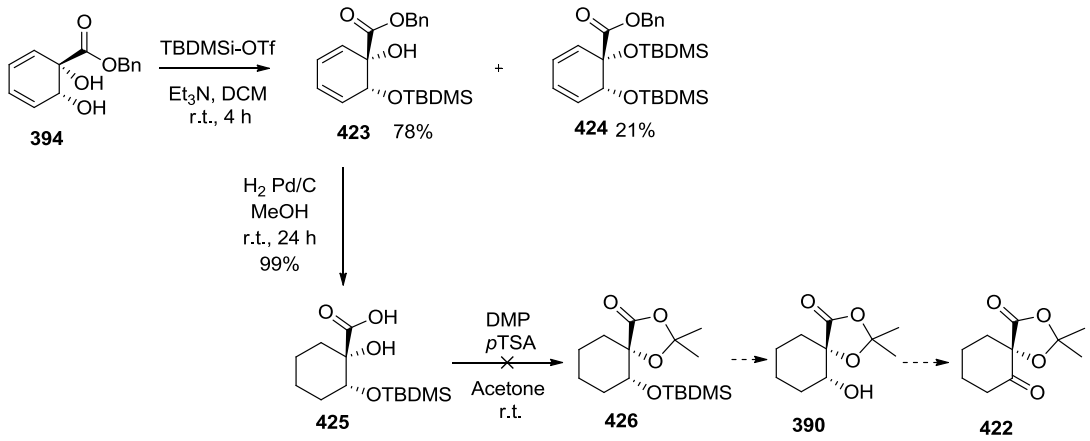


Scheme 127: Synthesis of ketone 422, shi analogue.

This new chiral ketone **422**, has many structural similarities with, and prerequisites of the Shi catalyst, as reviewed by Shi [184]

- The chiral control element has to be placed close to the reacting carbonyl to enhance the stereochemical interaction between substrate and catalyst.
- Fused rings and/or quaternary centre α to the carbonyl group being used to minimize epimerization of the stereogenic centres.
- Approach of an olefin to the reacting dioxirane being directed by sterically blocking one face or by a C_2 or pseudo–C_2–symmetric element.
- The carbonyl being inductively activated by introduction of an electron withdrawing element.

Rather than obtaining the catalyst **422** as the low yielding byproduct of the basic hydrolysis of **388**, a synthetic route was proposed to specifically target **422**. Scheme 128.



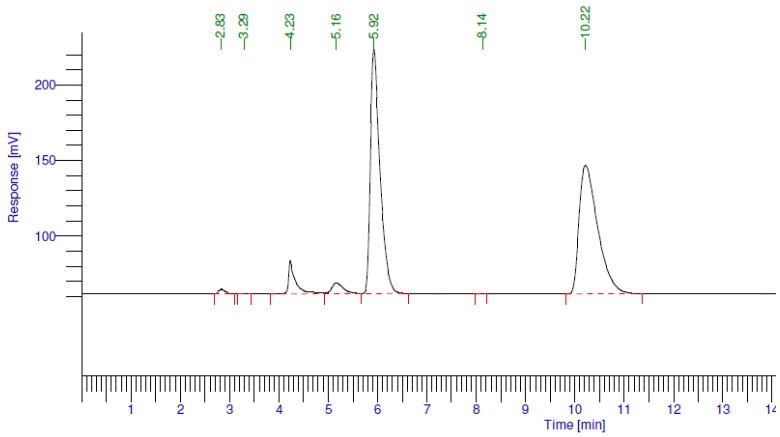
Scheme 128: Synthetic route through to chiral ketone 422.

Previously synthesised benzyl ester diene diol **394** was subjected to TBDMS-OTf silylation, in order to form the desired singly protected silyl **423** in a 78% yield. The di-silyl protected byproduct **424** was isolated and identified.

Silyl benzyl ester **423** was subjected to hydrogenation to simultaneously reduce the alkenes and cleave the benzyl ester to give **425** in near quantitative yields.

Attempts to form the acetonide protected compound **426** were unsuccessful on several attempts, utilising varying ratios of reagents and heating. The inability to form **426** could be attributed to the presence of the acid side chain. Acetonides are more commonly used to protect alcohols and diols, carboxylic acid protection is less precedented. Additionally autocatalytic deprotection could be preventing the reaction from occurring as we have seen reoccurring with compounds from the previous chapter.

It was considered that this new chiral ketone **422** may be able to act in a similar mode to the Shi catalyst in the asymmetric epoxidations of alkenes. To evaluate this, *trans*-stilbene **427** was chosen as a substrate it gives good yields (77-91%) and enantioselectivity (94-98% *ee*) in Shi's work.[184,223] Additionally the substrate was chosen as stilbene oxide **428** is easily separable via chiral HPLC. Graph 12. This circumvents the issue encountered in the previous chapter of poor quality HPLC traces of styrene oxide.



Graph 12: HPLC method for *trans*-stilbene oxide. Chiralcel OD. 1.0 mlmin^{-1}. 10% IPA/Hexane, 254nm. gave good baseline separation and peaks of equal integration at t_1 = 5.9 mins and t_2 = 10.2 mins.

Chiral ketone catalyst **422** was evaluated under the conditions described in Shi's most recent work[224] following the Oxone procedure.

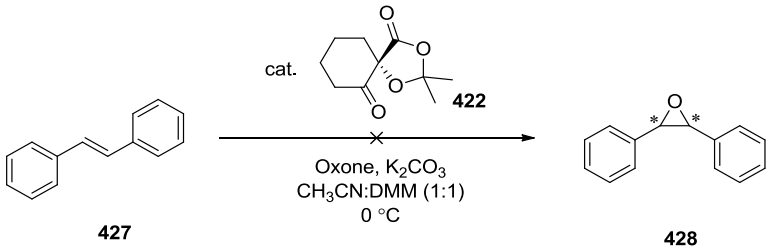


Figure 39: Epoxidation of *trans*-stilbene with chiral ketone 422. Reagents and Conditions: *trans*-stilbene (90 mg, 0.5 mmol), ketone **422** (14 mg, 10 mol%), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.03 mmol) in MeCN-DMM (v/v, 1/2) (9 mL) was added buffer (0.05 M aq Na_2HPO_4-0.05 M aq KH_2PO_4, pH 7.0) (3 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.212 M in 4×10^{-4} M aq EDTA, 4.8 mL) and a solution of K_2CO_3 (0.42 M in 4×10^{-4} M aq EDTA, 4.8 mL) were added dropwise over 1 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

Disappointingly the above reaction was unsuccessful, with complete recovery of *trans*-stilbene.

The Oxone methodology is known to be particularly sensitive to experimental procedure, Shi states [184,225] that it is essential for the Oxone and K_2CO_3 to be added simultaneously and constantly, ideally via two separate syringe pumps, to control and maintain a constant pH to prevent decomposition of either the Oxone or the chiral catalyst.

7.2 Catalyst Design #2

As the above synthetic route is deemed implausible, we sought a new catalyst design, **429**, for ease of synthesis and greater similarity to the Shi catalyst **344**. Figure 40.

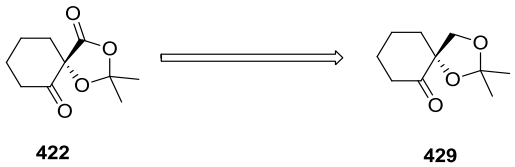
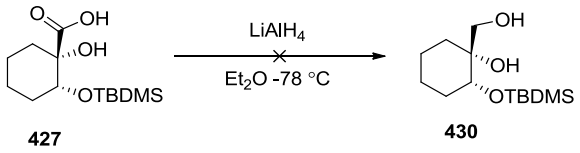


Figure 40: New catalyst design.

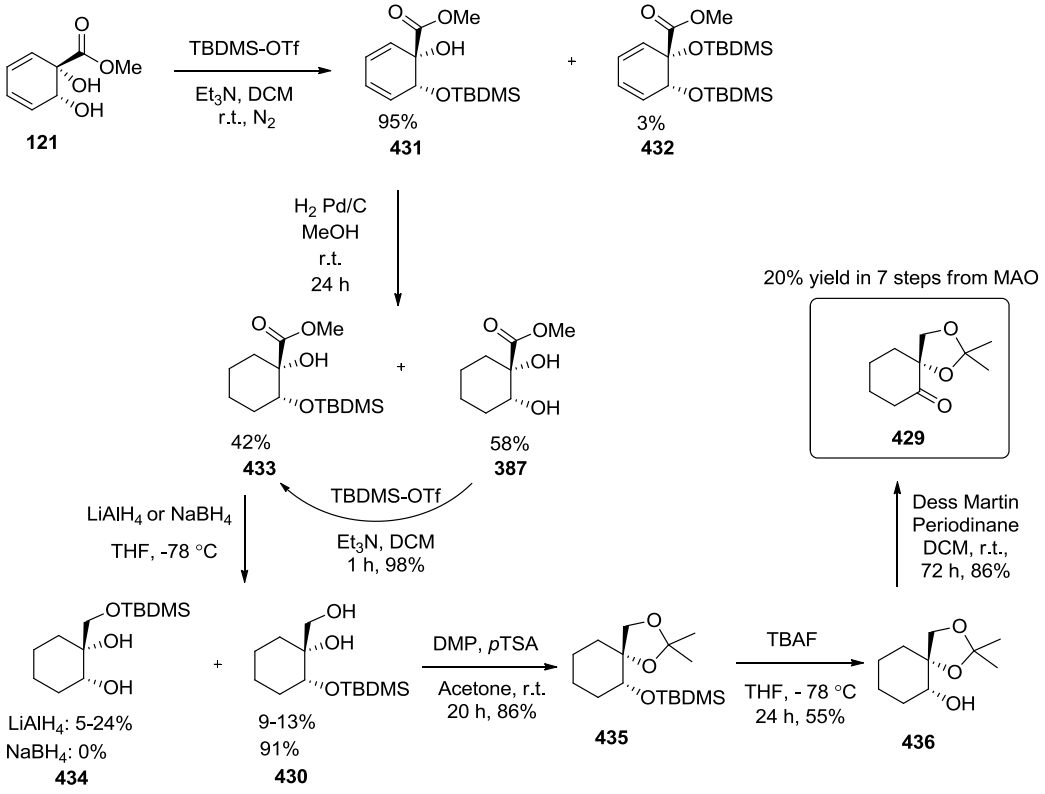
Since silyl alcohol acid **427** was in hand, synthesis of reduced diol **430** was attempted. Attempts using $LiAlH_4$ were unsuccessful with complete consumption of **427** to form complex inseparable mixtures. Scheme 129.



427 430

Scheme 129: Attempted reduction of 427.

As it has proven difficult to reduce the carboxylic acid **427**, a new synthetic route was devised to form the reduced alcohol side chain from an ester, as this has literature precedent.[68,69,72,75,144,207] Scheme 130.



Scheme 130: Catalyst Synthesis.

Known methyl ester **121** was converted to the desired singularly protected silyl methyl ester **431**, in improved selectivity (98% yield) compared to the benzyl ester analogue **425** (78% yield). Diene **431** was subjected to standard hydrogenation conditions to give the desired product **433** in 42% and the deprotected diol **387** in

58% yield as the major product. Diol methyl ester **387** was easily converted back to the desired silicon protected ester **433** in near quantitative yields, 98%.

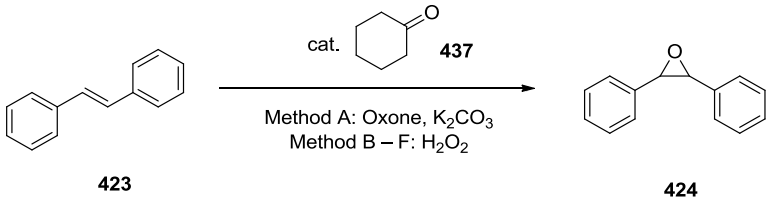
Reduction of silicon protected methyl ester **433** was attempted under various conditions, DIBAL-H was unsuccessful, $LiAlH_4$ proved too harsh as resulted in low yields, and formation of rearrangement product **434** , observed in varying ratios. Milder $NaBH_4$ proved most successful and selective giving 91% yield of desired diol **430**. Now with the reduced side chain in hand, acetonide protection formed the expected acetonide **435**. Silicon deprotection under standard TBAF conditions gave **436** in 53% yield.

Finally mild oxidation attempts to form the desired ketone using PDC were unsuccessful. Swern conditions proved to work, albeit in a 30% yield of **429**. More successfully Dess Martin Periodinane gave high yields of 86% of **429**, although over a 3 day period.

The chiral ketone **429** has been synthesized in 20% overall yield in 7 steps from MAO product. **429** has been fully characterised and matches known literature data of the opposite enantiomer, which has never been evaluated as a catalyst; the enantiomer **429** synthesised here has not been previously reported.[226]

7.3 Catalyst Testing

In order to minimise unnecessary waste of chiral catalyst **429** and to ensure well practiced experimental procedures, preliminary epoxidations reactions were carried out using cyclohexanone as an achiral analogue. Scheme 131, Table 9. Findings are discussed below.



Scheme 131: Epoxidation of *trans*-Stilbene under various conditions.

Reaction	Method	Conversion	Notes
T 1[227]	A	9%	Cyclohexanone – Oxone.
T 2[193]	B	4%	Cyclohexanone – H_2O_2
T 3[194]	C	0%	Cyclohexanone – H_2O_2 – *n*BuOH
T 4[193]	D	13%	Cyclohexanone – H_2O_2 – CH_2Cl_2 – cryostat used.

Table 9: Method A: *trans*-stilbene (180 mg, 1.0 mmol), cyclohexanone (0.03 mL, 30 mol%), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.04 mmol) in MeCN-DMM (v/v, 1:2) (15 mL) was added buffer (10 mL, 0.05 M aq $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aq Na_2(EDTA)). The mixture was cooled to 0 °C in an ice bath. A solution of Oxone (1.0 g, 1.6 mmol in 6.5 mL 4×10^{-4} M aq Na_2(EDTA)), and a solution of K_2CO_3 (0.93 g, 6.74 mmol H_2O 6.5 mL), were added dropwise separately and simultaneously via syringe pump over 2 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. **Method B:** To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and cyclohexanone (0.03 mL, 30 mol%) in MeCN-DMM (v/v, 1:2) (6 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq Na_2(EDTA)). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C. The reaction was left to room temperature over 48 h. Reaction was quenched and extracted as per Method A. **Method C:** To a solution of *trans*-stilbene (180 mg, 1.0 mmol), cyclohexanone (0.03 mL, 30 mol%), MeCN (0.2 mL, 3.8 mmol), *n*-BuOH (3.0 mL) was added buffer solution (3.5 mL, 0.3 M K_2CO_3 in 4×10^{-4} M aq Na_2(EDTA)). Followed by H_2O_2 (35%, 0.25 mL, 3 mmol) at 0 °C and left to warm to room temperature over 24 h. Reaction was quenched and extracted as per Method A. **Method D:** To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and cyclohexanone (0.03 mL, 30 mol%) in MeCN-EtOH- CH_2Cl_2 (v/v, 1:1:2) (2.0 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq Na_2(EDTA)). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C for 24h. Reaction was quenched and extracted as per Method A.

T 1, Method A, followed the Shi precedent for the use of Oxone and K_2CO_3 to form *insitu* dioxiranes. In this instance solutions of Oxone and K_2CO_3 were added separately and simultaneously via syringe pump, as stipulated by Shi.[227] Despite following this stringent procedure observed conversions were extremely low, 9%. This suggests that either cyclohexanone is not an active epoxidations catalyst or that the procedure is more sensitive to experimental error than originally considered. Considering this, subsequent reactions **T 3** – **T 4,** methods B – D,

followed Shi's hydrogen peroxide methodology. A more recent development, 1999 – 2007,[193-195,228] indicates that the hydrogen peroxide methodology is simpler and easier to perform, eliminating the use for syringe pumps, with effective mixing being highlighted as the only stipulated experimental requirement. Additionally as discussed in introductory sections, hydrogen peroxide is considered to be a green and sustainable oxidant.

Comparing the hydrogen peroxide methods **T 3 – T 4**, differences includes the variations in solvent choice; this was found to have little effect on reactivity and conversions. The best conversion was observed with method D, where additionally the temperature of the reaction was maintained at 0 °C with use of a cryostat. This suggests that temperature is an extremely influential factor.

In conclusion it seems that cyclohexanone, under the above reaction conditions, is an ineffective epoxidations catalyst. It was decided that commercial available Shi catalyst would be used to test the experimental reproducibility of the Shi methodology, and would be later used for a direct comparison to any epoxidations using synthesised chiral ketone **429**. Table 10.

Direct comparison of the Shi catalyst and cyclohexanone **T 5** indicated that the correct experimental procedures were being followed, as the Shi catalyst showed complete conversion, as in accordance with the literature values.[193] However cyclohexanone remained an inactive catalyst.

Reaction	Procedure	Conversion	Notes
T 5.1	D	100%	Shi 30 mol%
T 5.2	D	0%	Cyclohexanone
T 6.1	E	38%	Shi 15 mol%
T 6.2	E	0%	Catalyst **429** 15 mol%
T 7.1	F	0%	Catalyst **429** 1 equiv
T 7.2	F	0%	Cyclohexanone 1 equiv

Table 10: Method D: To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and catalyst (30 mol%) in MeCN-EtOH- CH_2Cl_2 (v/v, 1:1:2) (2.0 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M

aq $Na_2(EDTA)$). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C for 24h. Reaction was quenched and extracted as Method A. **Method E:** To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and catalyst (15 mol%) in MeCN-EtOH- CH_2Cl_2 (v/v, 1:1:2) (2.0 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq $Na_2(EDTA)$). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C for 24h. Reaction was quenched and extracted as Method A. **Method F:** To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and catalyst (1 equiv) in MeCN-EtOH- CH_2Cl_2 (v/v, 1:1:2) (2.0 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq $Na_2(EDTA)$). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C for 72 h. Reaction was quenched and extracted as Method A.

T 6 directly compared the Shi catalyst and the synthesised chiral ketone catalyst **429** at a 15 mol% catalyst loading (due to amount of material available). Disappointingly chiral ketone **429** displayed no conversion. Results either indicated that the chiral catalyst **429** is an inactive epoxidation catalyst, or is not as active as the Shi catalyst and higher catalyst loadings need to be considered. As is the case with the Shi catalyst, by reducing the catalyst loading by half, the conversion from **T 5.1** – **T 6.1** has reduced from 100% – 38%, a significant reduction.

Finally, **T 7** reactions were performed for length (3 days), using excess catalyst (1 equiv) and a maintained temperature (0 °C). These conditions should test whether chiral ketone **429** is in any way active. Cyclohexanone was also evaluated for comparison under these conditions. Disappointingly results indicated no conversion in either case.

From all of the above results it can be suggested that chiral ketone catalyst **429** is an inactive catalyst under the Shi hydrogen peroxide conditions. For completeness original Oxone conditions should be re-evaluated. Table 11.

Reaction	Procedure	Conversion	Notes
T8.1	A	65%	Shi 30 mol%
T8.2	A	0%	Chiral Ketone **429** 30 mol% 72 h

Table 11: Method A: *trans*-stilbene (180 mg, 1.0 mmol), cyclohexanone (0.03 mL, 30 mol%), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.04 mmol) in MeCN-DMM (v/v, 1:2) (15 mL) was added buffer (10 mL, 0.05 M aq $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aq $Na_2(EDTA)$). The mixture was cooled to 0 °C in an ice bath. A solution of Oxone (1.0 g, 1.6 mmol in 6.5 mL 4×10^{-4} M aq $Na_2(EDTA)$), and a solution of K_2CO_3 (0.93 g, 6.74 mmol H_2O 6.5 mL), were added dropwise separately and simultaneously via syringe pump over 2 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The above results **T 8** indicate that, as expected, the Shi catalyst epoxidises *trans*-stilbene with comparable yields to the literature (63 – 85% yield).[188] Chiral ketone reaction **T 8.2** performed under the same conditions, with the exception of time (as literature precedent suggest carbocycles are less active catalysts, the reaction was left for 72h at 0 °C)[185] gave no conversion. Interestingly, in comparison to the other chiral ketone hydrogen peroxide reactions, **T 6.2** and **T 7.1,** in this instance no chiral catalyst or potential byproducts were recovered. This could indicate decomposition, and possible reason why the reaction did not work.

7.4 Conclusion

It can be concluded that the chiral catalyst **429** is an inactive epoxidations catalyst. Additionally it can be suggested that the endocyclic oxygen present within the Shi catalyst is important to its catalytic activity as indicated in many of Shi's carbocyclic studies. [185]

Despite this novel chiral ketone **429** has been successfully synthesised in 8 steps in 20% overall yield from the MAO product.

Further elaboration and scope would intuitively follow adaption of the chiral ketone to make it a more active catalyst, including addition of electron withdrawing groups, potentially acetates or fluorine, as from the literature these have been shown to be viable.

8 Chapter 8: Conclusions and Future Work

This thesis details the application of the underexploited *ipso, ortho* diene *cis*-diol from the fermentation of benzoic acid by mutant strains of bacteria which contain benzoate dioxygenase enzymes.

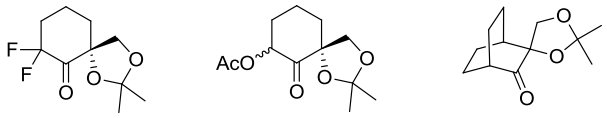
Within Chapter 2 the synthesis of novel aminocyclitols architectures is detailed. Unfortunately the compounds synthesised proved to be biologically inactive for the specific application of glycosidase inhibition. Despite this the work details novel methodology through to compounds containing six contiguous stereocenters, all imparted via substrate control.

The subsequent cyclitol section, Chapter 3, sought to synthesise the fully oxygenated counterparts. Despite a literature precedent the work led to complex mixtures of structurally similar compounds which proved difficult to isolate and purify. However a small quantity of one compound was isolated and structural identity and conformation alluded to.

Further work in these two areas would involve the synthesis of further aminocyclitol and cyclitol analogues, with specific interest and investigation into the controlled ring opening of epoxides and aziridines to avoid the complex mixtures and purification issues. Targets would be tested for a range of biological activities, as we have seen many applications through the literature sections of this work.

Chapter 4 completed and concluded some previous academic work, and highlights the synthetic utility of bromine substituted *ipso, otho* diene *cis*-diols. Further work in this area would explore the substrate scope and find the structural tolerances of the bacteria. It may be beneficial to engineer the bacteria so that it can tolerate different substrates, for example hetero-aromatics would be an interesting substrate (e.g. pyridine) as the nitrogen will already be present within the system, nitrogen insertion methodologies may be circumvented.

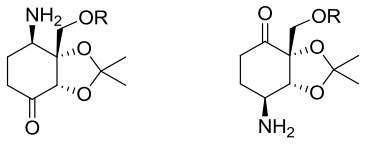
Finally the last section within this thesis, Chapter 6 and 7, investigated the viability of chiral acids and ketones derived from MAO as asymmetric epoxidation catalysts. Both the Miller[203] and Shi[184] precedent have been followed. There is vast scope for further investigation within this topic. Further manipulations and additions to the chiral substrates and further investigation into reaction conditions would, as the literature precedent suggests, yield comparative yields and selectivities. Structures **438** – **440** would be interesting targets, as we have seen electron withdrawing substituents enhance catalyst activity towards Oxone reagents and formation of the dioxirane intermediate. Scheme 132.



438 **439** **440**

Scheme 132: Future chiral catalyst targets.

Additional future work might scope the viability of oxidising azacarbasugar or cyclitol motifs towards chiral ketones such as **441** and **442** for the use in catalytic asymmetric epoxidations.



441 **442**

Scheme 133: Chiral ketones derived from azacarbasugars.

Overall this thesis has scratched the surface of the proposed applications for the underexploited MAO product. Future work would continue these efforts.

Overall this thesis has scratched the surface of the proposed applications for the underexploited MAO product. Future work would continue these efforts.

9 Experimental

9.1 General

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. In most cases, solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All other solvents were purchased as "anhydrous" grade from Fisher Scientific. "petrol" refers to petroleum spirit b.pt. 40-60 °C.

TLC was performed using aluminium backed plates precoated with Alugram®SIL G/UV 254nm. Visualization was accomplished by UV light and/or $KMnO_4$ followed by gentle warming. Organic layers were routinely dried with anhydrous $MgSO_4$ and evaporated using a Büchi rotary evaporator. When necessary, further drying was facilitated by high vacuum.

Flash column chromatography was carried out using Davisil LC 60Å silica gel (35-70 micron) purchased from Fisher Scientific.

IR spectra were recorded on Perkin-Elmer 1600 FT IR spectrometer with only selected absorbances quoted as ν in cm^{-1}. NMR spectra were run in $CDCl_3$ (unless otherwise specified) on Bruker Avance 250, 300, 400 or 500 MHz instruments at 298 K. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dq, doublet of quartets; td, triplet of doublets; m, multiplet and br, broad. *J* values are quoted to the nearest 0.5 Hz.

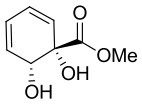
A micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 HPLC system (Agilent Technologies, Waldbronn, Germany).

The HPLC system was used as an autosampler only. 10µl of sample was injected into a 30:70 flow of water:acetonitrile at 0.6mL/min to the mass spectrometer. For each acquisition 10µL of calibrant of 5mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

X-Ray crystallography was recorded on a Nonius Kappa CCD diffractometer with Mo-Kα radiation (λ=0.71074Å). All structures were solvent by direct methods and refined on all F2 data using SHELX-97 suite of programs. Enantiomeric excess was measured using a Perkin Elmer 200 Series HPLC machine fitted with a Chiralcel AS column (25 cm), eluting with HPLC grade hexane and isopropylalcohol.

9.2 Chapter 1 Aminocyclitols Experimental

9.2.1 (1*S*,6*R*)-methyl 1,6-dihydroxycyclohexa-2,4-dienecarboxylate



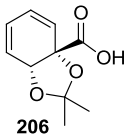
121

To a stirred solution of the microbial oxidation *cis* – diol acid **30** (982 mg, 6.3 mmol, 1 equiv) in MeOH/benzene (1:1, 30 mL) (trimethylsilyl)diazomethane (8 mL, 2.0 M in hexanes) was added dropwise until the yellow colour persisted and effervescence ceased. The solution was stirred for 2 h at room temperature then concentrated under reduced pressure to give crude **121** (1.06 g, 99%) as pale brown crystals, sufficiently pure to be used without further purification.

121 has been reported previously; spectroscopic data are in agreement with published values.[18]

R_f = 0.25 (50 % EtOAc-petrol); δ_H (250 MHz, $CDCl_3$) 6.10 (1H, dd, *J* = 10.0, 5.0 Hz, C=CH), 5.85 – 5.95 (1H, m, C=CH), 5.72 – 5.81 (2H, m, HC=CH), 4.81 (1H, s, CH(O)), 3.83 (3H, s, OCH_3);

9.2.2 (3a*S*,7a*R*)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylic acid



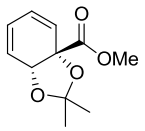
206

To diol acid **30** (1.77 g, 11.3 mmol, 1 equiv) and *para*-toluenesulfonic acid (5 mg, 0.3 mmol, 4 mol%) in acetone (50 mL), 2,2-dimethoxypropane (8.5 mL, 68.0 mmol, 6 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 24 h, transferred to a separating funnel, washed with saturated $NaHCO_{3(aq)}$ then extracted with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified via column chromatography (50% EtOAc–petrol) to give **206** (2.08 g, 94%) a pale yellow oil.

206 has been reported previously; spectroscopic data are in agreement with published values.[17]

R_f = 0.35 (50 % EtOAc-petrol); δ_H (250 MHz, $CDCl_3$) 6.21 – 6.11 (2H, m, C=CH), 6.05 – 5.98 (1H, m, C=CH), 5.83 – 5.78 (1H, m, C=CH), 4.94 (1H, d, *J* = 4.5 Hz (CH(O)), 1.49 (3H, s, CH_3), 1.43 (3H, s, CH_3);

9.2.3 (3a*S*,7a*R*)-methyl 2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3] dioxole-3a-carboxylate



113

To acetonide protected acid **206** (443 mg, 2.25 mmol, 1 equiv), *N,N'*-Dicyclohexylcarbodiimide (465 mg, 2.25 mmol, 1 equiv), in methanol (30 mL), *N,N*-Dimethylpyridin-4-amine (13 mg, 0.11 mmol, 5 mol %) was added. The resulting mixture was stirred at room temperature for 48 h. The reaction mixture was transferred to a separating funnel, diluted with EtOAc and washed with saturated brine. The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified via column chromatography (15% EtOAc–petrol) to give **113** (268 mg, 56%) as a pale yellow oil.

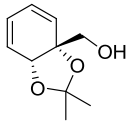
Or:

To methyl ester diol **121** (1.09 g, 6.45 mmol, 1 equiv) and *para*-toluenesulfonic acid (50 mg, 0.3 mmol, 4 mol%) in acetone (70 mL) 2,2-dimethoxypropane (5.5 mL, 40.0 mmol, 6 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 24 h, transferred to a separating funnel, washed with saturated $NaHCO_{3(aq)}$ then extracted with EtOAc (3 × 30 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified via column chromatography (15% EtOAc–petrol) to give **113** (1.30 g, 95%) as a pale yellow oil.

113 has been reported previously; spectroscopic data are in agreement with published values.[75]

R_f = 0.70 (60 % EtOAc-petrol); δ_H (250 MHz, $CDCl_3$) 5.85 – 6.02 (3H, m, C=CH), 5.66 – 5.74 (1H, m, C=CH), 4.84 (1H, d, *J* 2.5 Hz CH(O)), 3.66 (3H, s, OCH_3), 1.31 (3H, s, CH_3), 1.28 (3H, s, CH_3);

9.2.4 ((3aR,7aR)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxol-3a-yl)methanol



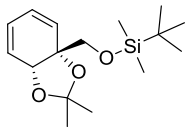
207

To methyl ester **113** (612 mg, 2.9 mmol, 1 equiv), lithium borohydride, 2M in THF, (1.45 mL, 2.91 mmol, 1 equiv) was added at -78 °C. The reaction mixture was stirred at -78 °C for 8 h, then left to warm to room temperature overnight. The reaction mixture transferred to a separating funnel, washed with saturated brine then extracted with EtOAc (4 × 25 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified via column chromatography (15% EtOAc–petrol) to give **207** (548 mg, 96 %) a pale yellow oil.

207 has been reported previously; spectroscopic data are in agreement with published values. [75]

R_f = 0.30 (50 % EtOAc-petrol); δ_H (250 MHz, $CDCl_3$) 5.91 – 6.06 (3H, m, C=CH), 5.63 (1H, d, *J* = 5 Hz, C=CH), 4.42 (1H, d, *J* = 5 Hz, CH(O)), 3.52 (1H, d, *J* = 10.0 Hz, C*H*H), 3.29 (1H, d, *J* = 10.0 Hz, CH*H*), 1.38 (3H, s, CH_3), 1.30 (3H, s, CH_3);

9.2.5 *tert*-butyl(((3a*R*,7a*R*)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxol-3a-yl)methoxy)dimethylsilane



208

To alcohol **207** (548 mg, 3.0 mmol, 1 equiv) dissolved in dichloromethane (30 mL), triethylamine (1.0 mL, 7.5 mmol, 2.5 equiv) was added and stirred at 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.83 mL, 3.6 mmol 1.2 equiv) was added dropwise at 0 °C over 5 mins. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was transferred to a separating funnel. Saturated brine (10 mL) was added, then extracted with EtOAc (3 × 10 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified via column chromatography (15% EtOAc-petrol) to give 47 (636 mg, 72%) as a colourless oil.

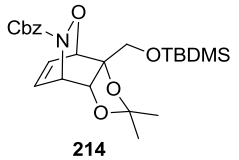
208 has been reported previously; spectroscopic data are in agreement with published values. [75]

R_f = 0.90 (10 % EtOAc-petrol); δ_H (250 MHz, $CDCl_3$) 6.10 – 5.94 (3H, m, C=CH), 5.67 (1H, d, *J* = 10.0 Hz, C=CH), 4.52 (1H, *J* = 5.0 Hz, CH(O)), 3.55 (1H, d, *J* = 12.0 Hz, C*H*H), 3.44 (1H, d, *J* = 12.0 Hz, CH*H*), 1.43 (3H, s, CH_3), 1.36 (3H, s, CH_3), 0.87 (9H, s, $C(CH_3)_3$), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$);

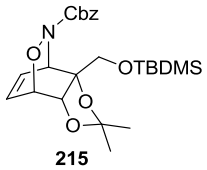
9.2.6 (3a*R*,4*R*,7*S*,7a*R*)-Benzyl 3a-(((*tert*-butyldimethylsilyl)oxy) methyl)-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-(epoxyimino)benzo[d][1,3]dioxole-8-carboxylate

and

9.2.7 (3a*R*,4*S*,7*R*,7a*R*)-benzyl 7a-(((*tert*-butyldimethylsilyl)oxy) methyl)-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-(epoxyimino)benzo[d][1,3]dioxole-8-carboxylate



214



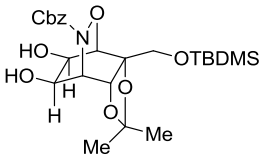
215

To a solution of diene **208** (446 mg, 1.5 mmol, 1 equiv) and tetrabutylammonium periodate (1.3 g, 3.0 mmol, 2 equiv) in dichloromethane (30 mL) at -78 °C was added *N*-(benzyloxycarbonyl)hydroxylamine (503 mg, 3.0 mmol, 2 equiv) in dichloromethane (10 mL) dropwise via cannula over 5 min. The reaction mixture was stirred at -78 °C under N_2 for 20 h, then diluted with EtOAc (10 mL) and washed with saturated aqueous sodium thiosulfate solution (5 mL) and then saturated brine (5 mL). The organic layer was separated and dried over $MgSO_4$, then concentrated under reduced pressure and purified by column chromatography (5% EtOAc-petrol) to give **214** (217 mg, 31%) as a colourless oil and **215** (403 mg, 58%) as a colourless oil.

214: R_f = 0.19 (15% EtOAc-petrol); $[\alpha]_D^{25}$ +1.53 (*c* 0.66 in CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.28 – 7.23 (5H, m), 6.46 (1H, br t, *J* = 5.0 Hz), 6.28 (1H, ddd, *J* = 7.5, 2.5, 1.5 Hz), 5.10 (1H, d, J_{AB} = 10.0 Hz), 5.06 (1H, dd, *J* = 6.0, 3.0 Hz) 5.02 (1H, d, J_{AB} = 10.0 Hz), 4.82 (1H, ddd, *J* = 6.0, 3.0, 1.5 Hz), 4.07 (1H, d, *J* = 3.0 Hz), 3.80 (1H, d, *J* = 12.0 Hz), 3.76 (1H, d, *J* = 12.0 Hz), 1.30 (3H, s), 1.21 (3H, s), 0.08 (9H, s), 0.01 (3H, s), -0.01 (3H, s); δ_C (75 MHz, $CDCl_3$) 158.2, 135.5, 132.4, 129.0, 128.4, 128.2, 128.0, 112.3, 84.0, 75.7, 72.2, 68.0, 66.2, 53.6, 28.0, 27.0, 25.9, 18.4, -5.5, -5.6; ν_{max} (film) 3515, 2929, 2857, 1747, 1713, 1497, 1455, 1379, 1312, 1284, 1248, 1211, 1184, 1151, 1097, 1061, 1024, 984, 929, 910, 776, 751, 731, 696, 616 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{24}H_{35}NO_6Si+Na)^+$, 484.2131; found 484.2140.

215: R_f = 0.28 (15% EtOAc-petrol); $[\alpha]_D^{25}$ +12.6 (*c* 0.87 in CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.37 – 7.29 (5H, s), 6.53 (1H, ddd, *J* = 7.5, 2.5, 1.5 Hz), 6.42 (1H, br t, *J* = 5.0 Hz), 5.22 (1H, d, J_{AB} = 12.0 Hz), 5.19 (1H, d, J_{AB} = 12.0 Hz), 5.06 (1H, ddd, *J* = 5.0, 5.0, 1.5 Hz), 4.89 (1H, dd, *J* = 5.0, 2.5 Hz), 4.18 (1H, d, *J* = 2.5 Hz), 3.90 (2H, s), 1.39 (3H, s), 1.28 (3H, s), 0.90 (9H, s), 0.09 (3H, s), 0.08 (3H, s); δ_C (75 MHz, $CDCl_3$) *δ* 157.5, 135.5, 131.1, 129.8, 128.4, 128.3, 128.1, 112.5, 84.1, 75.1, 71.5, 68.1, 65.6, 53.6, 28.3, 27.1, 26.0, 18.5, -5.3, -5.4; ν_{max} (film) 2930, 2857, 1748, 1709, 1498, 1462, 1380, 1370, 1327, 1295, 1248, 1214, 1170, 1150, 1096, 1080, 1065, 1026, 1005, 934, 904, 836, 776, 736, 696, 683, 670 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{24}H_{35}NO_6Si+Na)^+$, 484.2131; found 484.2108.

9.2.8 (3a*R*,4*R*,5*S*,6*R*,7*S*,7a*R*)-benzyl 3a-(((*tert*-butyldimethylsilyl) oxy)methyl)-5,6-dihydroxy-2,2-dimethylhexahydro-4,7-(epoxyimino)benzo[d][1,3]dioxole-8-carboxylate



216

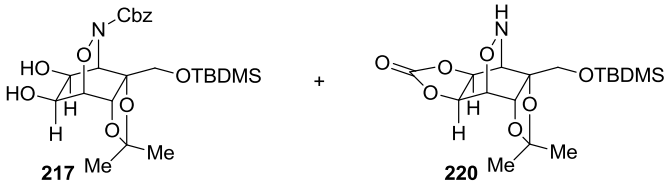
To alkene **214** (195 mg, 0.43 mmol, 1 equiv) in acetone:water (4:1, 20 mL) was added *N*-methylmorpholine *N*-oxide (57 mg, 0.43 mmol, 1.0 equiv) as a solid. Osmium tetroxide (2.5% in *tert*-butanol, 60 µL, 0.008 mmol, 2 mol%) was added via syringe and the reaction mixture was stirred at room temperature for 48 h. A colour change from colourless to pale yellow was observed. The reaction mixture was transferred to a separating funnel, diluted with EtOAc (15 mL) and washed with saturated aqueous sodium thiosulfate (5 mL) and saturated – (5 mL). The organic phase was separated and dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (50% EtOAc-petrol) to give **216** (172 mg, 81%), as a colourless oil.

R_f = 0.38 (40% EtOAc-petrol); $[\alpha]_D^{25}$ -27 (*c* 8.2 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 7.36-7.30 (5H, m), 5.18 (2H, s), 4.66 (1H, br s), 4.38 (1H, br s), 4.24-4.17 (3H, m), 3.82 (1H, d, *J* = 12.5 Hz), 3.75 (1H, d, *J* = 12.5 Hz) 3.75-3.63, (2H, m), 1.43 (3H, s), 1.40 (3H, s), 0.87 (9H, s), 0.04 (6H, s); δ_C (75 MHz, $CDCl_3$) 156.8, 135.4, 128.2, 128.1, 127.9, 111.1, 82.0, 78.0, 76.4, 72.3, 67.9, 64.9, 61.8, 61.2, 26.5, 26.4, 25.7, 18.2, -5.6, -5.7; ν_{max} (film) 3419, 2959, 2929, 2886, 2857, 1708, 1553, 1498, 1460, 1408, 1384, 1258, 1212, 1071, 836, 779 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{24}H_{37}NO_8Si+Na)^+$, 518.2186; found 518.2210.

9.2.9 (3a*R*,4*S*,5*S*,6*R*,7*R*,7a*R*)-benzyl 7a-(((*tert*-butyldimethylsilyl) oxy)methyl)-5,6-dihydroxy-2,2-dimethylhexahydro-4,7-(epoxyimino)benzo[d][1,3]dioxole-8-carboxylate

and

9.2.10 (3a*S*,4*S*,4a*R*,7a*R*,8*R*,8a*R*)-7a-(((*tert*-butyldimethylsilyl) oxy)methyl)-6,6-dimethylhexahydro-4,8-(epoxyimino)benzo[1,2-d:4,5-d']bis([1,3]dioxole)-2-one

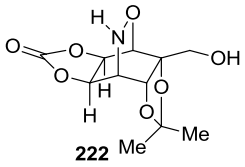


To alkene **215** (489 mg, 1.06 mmol, 1 equiv) in acetone:water (4:1, 20 mL) in a round-bottomed flask (50 mL) was added *N*-methylmorpholine *N*-oxide (143 mg, 1.06 mmol, 1 equiv) as a solid. Osmium tetroxide (2.5% in *tert*-butanol, 130 µL, 0.02 mmol, 2 mol%) was added via syringe and the reaction mixture was stirred at room temperature for 48 h. A colour change from colourless to pale yellow was observed and reaction mixture was transferred to a separating funnel, diluted with EtOAc (10 mL) and washed with saturated aqueous sodium thiosulfate (5 mL) then saturated brine (5 mL). The organic phase was separated and dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (50% EtOAc-petrol) to give **217** (230 mg , 44%) and **220** (70 mg, 17%) both as colourless oils. Also isolated was recovered starting material **215** (97 mg, 19%).

217: R_f = 0.36 (50 % EtOAc-petrol); $[\alpha]_D^{25}$ +17 (*c* 11.5 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 7.38 – 7.32 (5H, m), 5.20 (2H, s), 4.67 (1H, br s), 4.39 (1H, br s), 4.25 – 4.21 (3H, m), 3.84 (1H, d, *J* = 10.0 Hz), 3.78 (1H, d, *J* =10.0 Hz) 3.54 (1H, br s), 3.32 (1H, d, *J* = 5.0 Hz) 1.44 (3H, s), 1.42 (3H, s), 0.89 (9H, s), 0.06 (6H, s); δ_C (75 MHz, $CDCl_3$) 158.9, 135.5, 128.5, 128.3, 128.3, 111.7, 83.1, 76.2, 73.2, 68.3, 66.0, 62.5, 61.4, 58.9, 26.7, 26.6, 25.9, 18.4, -5.5, -5.6; ν_{max} (film) 3428, 2929, 2856, 1710, 1498, 1454, 1383, 1256, 1102, 1064, 835, 777 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{24}H_{37}NO_8Si+Na)^+$, 518.2186; found 518.2210.

220: R_f = 0.57 (50 % EtOAc-petrol); $[\alpha]_D^{25}$ -6.5 (*c* 3.5 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 6.06 (1H, br s), 5.03-5.02 (2H, m), 4.33 (1H, d, *J* = 6.0 Hz), 4.21 (1H, d, *J* = 6.0 Hz), 4.08 (1H, d, *J* = 12.0 Hz), 3.90 (1H, d, *J* = 12.0 Hz), 3.67 (1H, br s) 1.45 (3H, s), 1.44 (3H, s), 0.90 (9H, s), 0.09 (3H, s), 0.08 (3H, s); δ_C (75 MHz, $CDCl_3$) 154.4, 110.9, 81.8, 73.7, 71.7, 69.9, 68.3, 66.2, 53.4, 26.9, 26.6, 25.8, 18.3, -5.4, -5.5; ν_{max} (film) 3270, 2955, 2930, 2857, 1808, 1463, 1361, 1254, 1166, 1077, 836, 779 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{17}H_{29}NO_7Si+Na)^+$, 410.1611; found 410.1664.

9.2.11(3a*S*,4*R*,4a*R*,7a*R*,8*S*,8a*R*)-4a-(hydroxymethyl)-6,6-dimethyl hexahydro-4,8-(epoxyimino)benzo[1,2-d:4,5-d']bis([1,3] dioxole) -2-one

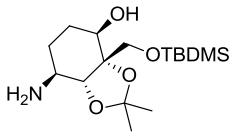


222

To silyl ether **216** (165 mg, 0.33 mmol, 1 equiv.) in THF (20 mL) at 0 °C was added tetrabutylammonium fluoride (0.3 mL, 1.0 M in THF, 1.0 equiv) dropwise over 5 min. The reaction mixture was stirred at 0 °C for 12 h, then transferred to a separating funnel and diluted with EtOAc (20 mL) and washed with water (2 x 10 mL). The organic phase was then washed further with saturated brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (50% EtOAc-petrol) to give **222** (34 mg, 24%), as a colourless oil.

R_f = 0.20 (50% EtOAc-petrol); $[\alpha]_D^{25}$ -1.5 (*c* 1.7 in $CHCl_3$); δ_H (250 MHz, $(CD_3)_2CO$) 6.88 (1H, br s), 5.16 (1H, dd, *J* = 8.0, 4.0 Hz), 5.09 (1H, d, *J* = 8.0 Hz), 4.42 (1H, d, *J* = 4.0 Hz), 4.27 (1H, t, *J* = 4.0 Hz), 4.19 (1H, br s), 3.97 – 3.84 (3H, m), 1.50 (3H, s), 1.48 (3H, s); δ_C (75 MHz, $(CD_3)_2CO$) 154.5, 110.1, 81.7, 73.7, 72.0, 70.6, 69.4, 64.5, 51.6, 25.8, 25.6; ν_{max} (film) 3268, 2992, 2923, 1800, 1780, 1454, 1369, 1165, 1067, 770 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{11}H_{16}NO_7+Na)^+$, 296.0746; found 296.0787.

9.2.12(3a*S*,4*R*,7*S*,7a*R*)-7-amino-3a-(((*tert*-butyldimethylsilyl) oxy)methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxol-4-ol

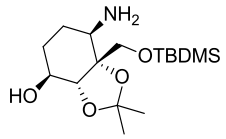


223

To alkene **214** (61 mg, 0.13 mmol, 1 equiv) in EtOAc (20 mL) was added palladium on carbon (6 mg, 10 wt%). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h then filtered through celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (50% EtOAc-petrol) to give **223** as a colourless oil (43 mg, 99%).

R_f = 0.85 (50% EtOAc-petrol); $[\alpha]_D^{25}$ -15 (*c* 0.55 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.05 (1H, d, *J* = 3.0 Hz), 3.97 (1H, d, *J* = 12.0 Hz), 3.83 (1H, d, *J* = 12.0 Hz), 3.80 (1H, app q, *J* = 3.0 Hz), 3.46-3.42 (1H, m, 1H), 2.76 (3H, br s), 2.02 – 1.87 (1H, m), 1.83 – 1.72 (2H, m), 1.61 – 1.51 (1H, m), 1.46 (3H, s), 1.37 (3H, s), 0.91 (9H, s), 0.10 (3H, s), 0.09 (3H, s); δ_C (75 MHz, $CDCl_3$) 108.1, 83.6, 80.1, 73.2, 65.1, 47.4, 28.1, 26.7, 25.9, 25.4, 24.5, 18.3, -5.5, -5.6; ν_{max} (film) 2961, 2927, 2854, 1590, 1519, 1463, 1392, 1300, 1251, 1215, 1151, 1033, 747 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{16}H_{33}NO_4Si+Na)^+$, 354.2076; found 354.2054.

9.2.13(3a*R*,4*S*,7*R*,7a*R*)-7-amino-7a-(((*tert*-butyldimethylsilyl)oxy) methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxol-4-ol

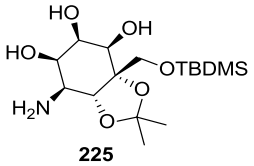


224

To alkene **215** (253 mg, 0.55 mmol, 1 equiv) in EtOAc (20 mL) was added palladium on carbon (26 mg, 10 mass%). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h then filtered through celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (20% MeOH-79% EtOAc-1% Et_3N) to give **224** as a colourless oil (179 mg, 98%).

R_f = 0.43 (20% MeOH-79% EtOAc-1% Et_3N); $[\alpha]_D^{25}$ -37 (*c* 3.5 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.03 (1H, br s), 3.96 – 3.93 (2H, m), 3.70 (1H, d, *J* = 11.0 Hz), 3.36 (3H, br s), 3.12 (1H, br s), 2.00 – 1.88 (1H, m), 1.82 – 1.72 (2H, m), 1.62 – 1.58 (1H, m), 1.41 (3H, s), 1.32 (3H, s), 0.88 (9H, s), -0.09 (6H, s); δ_C (75 MHz, $CDCl_3$) 108.4, 83.1, 79.8, 67.3, 65.8, 52.3, 27.5, 26.3, 26.0, 25.9, 23.7, 18.3, -5.3, -5.5; ν_{max} (film) 3282, 2898, 2930, 2856, 1472, 1378, 1250, 1216, 1087, 963, 835 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{16}H_{33}NO_4Si+Na)^+$, 354.2076; found 354.2076.

9.2.14(3a*S*,4*R*,5*R*,6*R*,7*S*,7a*R*)-7-amino-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-4,5,6-triol

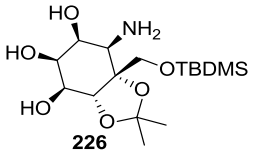


225

To diol **216** (28 mg, 0.06 mmol, 1 equiv) in EtOAc (20 mL) was added palladium on carbon (5 mg, 20 mass%). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h then filtered through celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% MeOH-89% chloroform-1% Et_3N) to give **225** as a colourless oil (11 mg, 50%).

R_f = 0.25 (15% MeOH-84% EtOAc-1% Et_3N); $[\alpha]_D^{25}$ +43 (*c* 0.6 in H_2O);); δ_H (300 MHz, D_2O) 4.46 – 3.93 (10H m), 1.45 (3H, s), 1.39 (3H, s), 0.92 (9H, s), 0.12 (6H, s); δ_C (75 MHz, $CDCl_3$) 108.9, 83.8, 74.3, 70.6, 67.6, 65.3, 64.7, 51.9, 29.6, 27.9, 26.6, 26.0, 25.9, 18.4, -5.3, -5.4; ν_{max} (film) 3324, 3256, 2965, 2813, 2787, 1432, 1376, 1244, 1156, 1020, 978, 836, 774 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{16}H_{33}NO_6Si+Na)^+$, 386.1907; found 386.1968.

9.2.15(3a*R*,4*S*,5*S*,6*S*,7*R*,7a*R*)-7-amino-7a-(((*tert*-butyldimethylsilyl) oxy)methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-4,5,6-triol

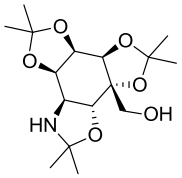


226

To diol **217** (120 mg, 0.24 mmol, 1 equiv) in EtOAc (20 mL) was added palladium on carbon (12 mg, 10 mass%). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h then filtered through celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (50% EtOAc-petrol) to give **226** as a colourless oil (39 mg, 45%).

R_f = 0.35 (50% EtOAc-petrol); $[\alpha]_D^{25}$ +33 (*c* 0.39 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.25 – 4.20 (2H, m), 4.18 – 4.15 (2H, m), 4.03 (1H, d, *J* = 15.0 Hz), 3.91 (1H, d, *J* = 15.0 Hz), 3.30 (1H, s), 1.46 (3H, br s), 1.43 (3H, s), 0.92 (9H, s), 0.11 (3H, s), 0.10 (3H, s); δ_C (75 MHz, $CDCl_3$) 110.3, 81.9, 73.8, 72.9, 66.7, 62.7, 60.2, 58.3, 26.8, 26.8, 25.9, 18.4, -5.3, -5.4; ν_{max} (film) 3404, 2958, 2930, 2857, 1463, 1382, 1255, 1210, 1101, 1060, 863, 779 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{16}H_{33}NO_6Si+H)^+$, 364.2155; found 364.2093.

9.2.16(4a*R*,7a*R*,8*S*,8a*R*,11a*R*,11b*R*)-2,2,6,6,10,10-hexamethylhexahydrobis([1,3]dioxolo)[4',5':2,3;4'',5'':5,6]benzo[1,2-d][1,3]dioxin-8-amine

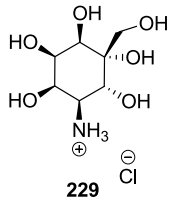


228

225 (38 mg, 0.1 mmol, 1 equiv) dissolved in THF (20 mL) was added TBAF (0.1 mL 1M in THF) was added at 0°C and stirred for 24 h. The resulting solution was extracted with water. The aqueous layer was concentrated down and contained the alcohol product and quaternary ammonium salts which could not be separated. The resulting oil was dissolved into acetone (20 mL) to which was added 2,2-dimethoxypropanol (2 mL, 16 mmol, 160 equiv), and *para*-toluenesulfonic acid (20 mg, 0.1 mmol, 1 equiv). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was transferred to a separating funnel, diluted with EtOAc, washed with saturated brine, dried over $MgSO_4$, concentrated under reduced pressure to give intermediate **228** a yellow oil (26 mg, 10%).

δ_H (300 MHz, $CDCl_3$) 4.98 (1H, d, *J* = 12.0 Hz), 4.42 – 4.65 (5H, m), 3.65 – 3.69 (2H, m), 1.36 – 1.44 (18H, m, CH_3); δ_C (75 MHz, $CDCl_3$); 101.5 ($C(CH_3)_2$), 109.6 ($C(CH_3)_2$), 90.2 ($NC(CH_3)_2$), 76.5 (CHO), 73.0 (CHO), 69.6 (CHO), 69.4 (CHO), 67.2 (CHN), 55.5 (CH_2), 29.8 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 26.1 ($C(CH_3)_2$), 25.7 ($C(CH_3)_2$), 20.6 ($C(CH_3)_2$); ν_{max} (film) 2994, 2933, 2864, 1459, 1381, 1252, 1211, 1072, 868 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_{16}H_{27}NO_6+H)^+$, 330.1917; found 330.1796.

9.2.17(1*S*,2*R*,3*R*,4*R*,5*R*,6*R*)-2,3,4,5,6-pentahydroxy-3-(hydroxymethyl)cyclohexanaminium chloride

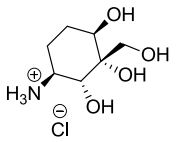


229

228 (26 mg, 0.08 mmol) was stirred in 1M HCl (20 mL) for 24 h at room temperature. The resulting mixture was concentrated under reduced pressure to give **229** (15 mg, 89%) a yellow oil unpurified.

$[\alpha]_D^{25}$ -32 (*c* 0.5, H_2O); δ_H (300 MHz, D_2O) 4.43 (1H, d, *J* = 6.0 Hz), 4.25 (1H, d, *J* = 9.0 Hz), 4.06 (1H, d, *J* = 6.0 Hz), 3.97 (1H, d, *J* = 6.0 Hz), 3.85 (1H, br s), 3.60 – 3.71 (2H, m); δ_C (75 MHz, D_2O) 76.3, 76.0, 72.8, 67.7, 66.6, 66.5, 60.3; ν_{max} (film) 3349, 2506, 1631, 1433, 1258, 1063 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_7H_{15}NO_6+H)^+$, 210.0978; found 210.0965.

9.2.18(1*S*,2*R*,3*S*,4*R*)-2,3,4-trihydroxy-3-(hydroxymethyl) cyclo hexanaminium chloride

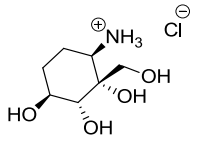


230

Hydroxyamine **223** (43 mg, 0.13 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with EtOAc (2 x 10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **230** as a colourless oil (26 mg, 94%).

$[\alpha]_D^{25}$ +22 (*c* 1.3 in H_2O); δ_H (300 MHz, D_2O) 3.85 (1H, s), 3.64 (1H, d, *J* = 12.0 Hz), 3.57 (1H, d, *J* = 12.0 Hz), 3.55 (1H, d, *J* = 9.0 Hz), 3.37 – 3.18 (1H, m), 1.80 – 1.55 (4H, m); δ_C (75 MHz, D_2O) 76.0, 69.9, 68.6, 63.5, 52.1, 25.8, 22.7; ν_{max} (film) 3336, 2981, 2482, 1602, 1383, 1233, 1156, 1069, 1021, 956, 797 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_7H_{15}NO_4+Na)^+$, 200.0898; found 200.0906.

9.2.19(1*R*,2*R*,3*R*,4*S*)-2,3,4-trihydroxy-2-(hydroxymethyl) cyclohexanaminium chloride

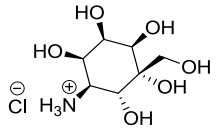


231

Hydroxyamine **224** (30 mg, 0.09 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with EtOAc (2 × 10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **231** as a pale yellow oil (17 mg, 88%).

$[\alpha]_D^{25}$ +35 (*c* 0.85 in H_2O); δ_H (300 MHz, D_2O) 3.86 (1H, d, *J* = 12.0 Hz), 3.81 (1H, td, *J* = 7.5, 4.0 Hz), 3.55 (1H, d, *J* = 12.0 Hz), 3.49 (1H, d, *J* = 6.0 Hz), 3.38-3.34 (1H, m), 1.92 – 1.63 (3H, m), 1.52 – 1.40 (1H, m); δ_C (75 MHz, D_2O) 74.1, 72.3, 69.8, 63.4, 54.0, 26.0, 22.8; ν_{max} (film) 3317, 2940, 2508, 1400, 1071, 1027, 972, 799 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_7H_{15}NO_4+H)^+$, 179.1157; found 179.1129.

9.2.20(1*S*,2*R*,3*R*,4*R*,5*R*,6*R*)-2,3,4,5,6-pentahydroxy-3-(hydroxymethyl)cyclohexanaminium chloride

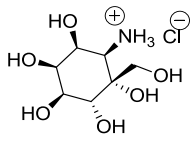


232

Aminotriol **225** (11 mg, 0.03 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with EtOAc (2 × 10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **232** as a colourless oil (8 mg, 99%).

$[\alpha]_D^{25}$ -47 (*c* 0.4 in H_2O); δ_H (300 MHz, D_2O) 4.24 (1H, q, *J* = 3.0 Hz), 4.04 – 3.99 (3H, m), 3.89 (1H, d, *J* = 12.0 Hz), 3.75 (1H, d, *J* = 12.0 Hz), 3.57 (1H, dd, *J* = 10.5, 3.0 Hz); δ_C (75 MHz, D_2O) 75.5, 72.6, 70.4, 65.6, 65.1, 62.8, 53.3; ν_{max} (film) 3302, 2958, 2511, 1629, 1508, 1077, 1028, 808, 723 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_7H_{15}NO_6+Na)^+$, 232.0797; found 232.0783.

9.2.21(1*R*,2*R*,3*R*,4S,5*S*,6*S*)-2,3,4,5,6-pentahydroxy-2-(hydroxymethyl)cyclohexanaminium chloride



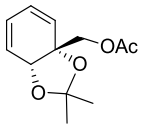
233

Triol **226** (35 mg, 0.1 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with EtOAc (2 × 10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **233** as a pale yellow oil (21 mg, 80%).

$[\alpha]_D^{25}$ +32 (*c* 0.5 in H_2O); δ_H (250 MHz, D_2O) *δ* 4.16 – 4.14 (2H, m), 3.91 (1H, d, *J* = 12.0 Hz), 3.83 – 3.70 (3H, m), 3.59 – 3.56 (1H, br t, *J* = 2.5 Hz); δ_C (75 MHz, D_2O) 75.9, 75.6, 72.4, 69.3, 66.3, 66.1, 59.9; ν_{max} (film) 3272, 2943, 2507, 1622, 1496, 1398, 1184, 1155, 1074, 1025, 928, 892, 814, 712 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $(C_7H_{15}NO_6+H)^+$, 210.0978; found 210.0965.

9.3 Chapter 2: Cyclitols Experimental

9.3.1 ((3a*R*,7a*R*)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxol-3a-yl)methyl acetate



274

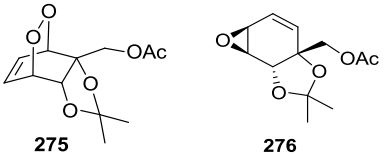
To a stirred solution of **207** (637 mg, 3.50 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added triethylamine (0.48 mL, 3.49 mmol, 1 equiv), DMAP (42 mg, 0.35 mmol, 10 mol%) and Ac_2O (0.33 mL, 3.50 mmol, 1 equiv). TLC indicated reaction was complete after 30 mins. Water (20 mL) was added to the reaction mixture and extracted with EtOAc (4 x 20 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (15% EtOAc-petrol) to yield pure **274** (600 mg, 77%) as a yellow oil.

R_f = 0.45 (15% EtOAc-petrol); $[\alpha]_D^{25}$ -81.6 (c 1.20, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 6.13 – 6.08 (1H, m, C=CH), 6.03 – 5.98 (2H, m, C=CH), 5.72 (1H, d, *J* = 10.0 Hz, C=CH), 4.41 (1H, d, *J* = 4.5 Hz, C(*H*)OC$(CH_3)_2$), 4.15 (1H, d, J_{AB} = 11.5 Hz, CH_2), 3.94 (1H, d, J_{AB} = 11.5 Hz CH_2), 2.07 (3H, s, OAc), 1.44 (3H, s, CH_3), 1.37 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 170.6 (C=O), 128.1, 125.4, 124.3, 123.1 (C=C), 106.6 (*C*$(CH_3)_2$), 78.3 (*C*O(CH_2)), 71.8 (*C*(H)OC$(CH_3)_2$), 66.1 (CH_2), 27.1, 26.4 (C(*C*$H_3)_2$), 20.8(C=O*C*H_3); ν_{max} (film) 2991, 2937, 1741, 1415, 1372, 1239, 1172, 1043, 906, 728, 648 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{12}H_{16}O_4+Na)^+$, 247.0946; found 247.0931.

9.3.2 ((3a*R*,4*R*,7*S*,7a*R*)-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-epidioxybenzo[d][1,3]dioxol-3a-yl)methyl acetate

and

9.3.3 ((2a*S*,4a*R*,7a*R*,7b*R*)-6,6-dimethyl-2a,4a,7a,7b-tetrahydro-[1,2]dioxeto[3',4':3,4]benzo[1,2-d][1,3]dioxol-4a-yl)methyl acetate



275 **276**

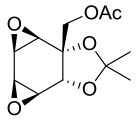
To a stirred solution of **274** (94 mg, 0.42 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added a solution of 5,10,15,20-Tetraphenyl-21H,23H-porphine (10 mg, 0.016 mmol, 4 mol%) in CH_2Cl_2 (50 mL) dropwise over a period of 18 h, while the solution irradiated with 150 W halogen lamps, and being continually sparged with oxygen. After 18 h no more conversion was observed; the solution was concentrated under reduced pressure and purified via flash column chromatography (15% EtOAc-petrol) to yield pure **275** (52 mg, 48%) as a colourless oil, by product **276** a pale pink oil (10 mg, 9%) and r.s.m **274** (11 mg, 12%).

275: R_f = 0.35 (15% EtOAc-petrol); $[\alpha]_D^{25}$ -16.9 (*c* 0.83, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 6.65 (1H, t, *J* = 8.0 Hz, C=CH), 6.55 (1H, t, *J* = 8.0 Hz, C=CH), 4.88-4.91 (2H, m, C(H)O), 4.55 (1H, d, J_{AB} = 12 CH_2), 4.31 (1H, d, J_{AB} = 12 CH_2), 4.25 (1H, d, *J* = 4.8 Hz, C(*H*)OC$(CH_2)_3$), 2.13 (3H, s, C=OCH_3), 1.39 (3H, s, CH_3), 1.30 (3H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 170.4 (C=O), 131.5 (C=C), 130.3 (C=C), 122.3 (*C*$(CH_3)_2$), 79.9 (*C*O(CH_2), 74.6 (*C*(H)OC$(CH_3)_2$), 72.1 (*C*HO-O), 71.8 (*C*HO-O), 65.9 (CH_2), 27.8 (C(*C*$H_3)_2$), 26.8 (C(*C*$H_3)_2$), 20.8 (CO*C*H_3); ν_{max} (film) 2995, 2988, 2928, 1736, 1348, 1372, 1450, 1244, 1204, 1144, 1039, 919, 743, 712, 644 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{12}H_{16}O_6+Na)^+$, 279.0844; found 279.0829.

Byproduct **276**: R_f = 0.40 (15% EtOAc-petrol); $[\alpha]_D^{25}$ –14.3 (*c* 0.28, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 6.09 (1H, dd, *J* = 10.0, 4.0 Hz, HC=C*H*CO), 5.70 (1H, dt, *J* = 10.0 1.5 Hz, *H*C=CHCO), 4.65 (1H, t, *J* = 1.0 Hz, C*H*OC$(CH_3)_2$), 4.33 (1H, J_{AB} = 11.0 Hz, CH_2), 3.83 (1H, J_{AB} = 11.0 Hz, CH_2), 3.64 (1H, dd, *J* = 3.5, 2.5 Hz, C*H*(O)), 3.35 – 3.38 (1H, m,

C*H*(O)), 2.09 (3H, s), 1.41 (3H, s), 1.37 (3H, s); δ_c (75 MHz, $CDCl_3$) 170.4 (C=O), 132.5 (C=*C*C(O)CH_2, 124.1 (C=*C*CH(O)), 110.5 (*C*$(CH_3)_2$) , 79.0 (*C*O(CH_2), 71.3 (*C*(H)OC$(CH_3)_2$), 66.8 (CH_2), 50.3 (*C*H(O-O)CH(O)), 46.5 (*C*H(O-O)CH=CH), 27.8, 26.6 (CH_3), 20.8 (C=OCH_3); ν_{max} (film) 2989, 2943, 1745, 1455, 1379, 1236, 1181, 1162, 1089, 1060, 1042, 989, 829, 721 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{12}H_{16}O_5+Na)^+$, 263.0895; found 263.0903.

9.3.4 ((1a*R*,1b*R*,2a*R*,2b*S*,5a*R*,5b*S*)-4,4-dimethylhexahydrobis (oxireno)[2',3':3,4;2'',3'':5,6]benzo[1,2-d][1,3]dioxol-2b-yl)methyl acetate

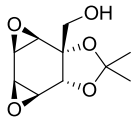


281

To a stirred solution of **275** (755 mg, 2.94 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added 5,10,15,20-Tetraphenyl-21H,23H-porphine cobalt(II) (11 mg, 0.01 mmol, 6 mol%). The solution was stirred for 30 mins, until TLC indicated full conversion of **275**. The solution was concentrated under reduced pressure and purified via flash column chromatography (15% EtOAc-petrol) to yield pure **281** (724 mg, 96%) as a colourless oil.

R_f = 0.15 (15% EtOAc-petrol); $[\alpha]_D^{25}$ -33.8 (*c* 0.80, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 4.35 (1H, d, J_{AB} = 11.0 Hz, CH_2), 4.32 (1H, d, *J* = 2.0 Hz, C(*H*)OC$(CH_2)_3$), 4.02 (1H, d, J_{AB} = 11.0 Hz, CH_2), 3.58 (1H, t, *J* = 3.0 Hz), 3.52 (1H, t, *J* = 3.0 Hz), 3.39 (1H, dd, *J* = 3.0, 2.0 Hz), 3.04 (1H, d, *J* = 3.5 Hz), 2.11 (3H, s, C=OCH_3), 1.43 (3H, s, CH_3), 1.42 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 170.4 (C=O), 110.4 (*C*$(CH_3)_2$), 78.3 (*C*O(CH_2), 71.9 (*C*(H)OC$(CH_3)_2$), 65.5 (CH_2), 51.5 (*C*(H)O), 50.9 (*C*(H)O), 47.6 (*C*(H)O), 47.5 (*C*(H)O), 28.0 (C(*C*$H_3)_2$), 26.3 (C(*C*$H_3)_2$), (C(*C*$H_3)_2$), 20.8(C=O*C*H_3); ν_{max} (film) 2991, 2938, 1742, 1455, 1435, 1380, 1231, 1175, 1063, 1043, 992, 964, 803, 630 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{12}H_{16}O_6+Na)^+$, 279.0844; found 279.0861.

9.3.5 ((1a*R*,1b*R*,2a*R*,2b*S*,5a*R*,5b*S*)-4,4-dimethylhexahydrobis (oxireno)[2',3':3,4;2'',3'':5,6]benzo[1,2-d][1,3]dioxol-2b-yl)methanol

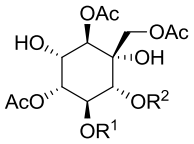


272

To a stirred solution of **281** (23 mg, 0.089 mmol, 1 equiv) in MeOH (10 mL), NH_3 was continuously bubbled through the solution for 10 h. After TLC indicated consumption of all starting material the solution was concentrated under reduced pressure and purified via flash column chromatography (50% EtOAc-petrol) to yield pure **272** (18 mg, 95%) as a colourless oil.

R_f = 0.20 (50 % EtOAc-petrol); $[\alpha]_D^{25}$ -46 (c 1.02, CH_2Cl_2); δ_H (250 MHz, $CDCl_3$) 4.41 (1H, d, *J* = 2.0 Hz, C(*H*)OC$(CH_2)_3$), 3.77 (1H, d, J_{AB} = 11.0 Hz, CH_2), 3.61 (1H, d, J_{AB} = 11.0 Hz, CH_2), 3.57 (1H, d, *J* = 3.0 Hz C(H)O), 3.53 (1H, d, *J* = 3.5 Hz, C(H)O), 3.41 (1H, dd, *J* = 3.5, 2.0 Hz, C(H)O), 3.04 (1H, dd, *J* = 3.5, 2.0 Hz, C(H)O), 2.09 (3H, br s, OH), 1.44 (6H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 110.0 (*C*$(CH_3)_2$), 79.4 (*C*O(CH_2), 71.5 (*C*(H)OC$(CH_3)_2$), 64.4 (CH_2), 51.7 (*C*(H)O), 51.4 (*C*(H)O), 47.6 (*C*(H)O), 47.5 (*C*(H)O), 28.1 (CH_3), 26.5 (CH_3); ν_{max} (film) 3491, 2982, 2253, 1457, 1383, 1247, 1219, 1080, 1063, 907, 726, 647 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{10}H_{14}O_5+Na)^+$, 237.0734; found 237.0792.

9.3.6 Compound 290A



R^1 = H, R^2 = Ac
or
R^1 = Ac, R^2 = H
290A

281 (94 mg, 0.36 mmol, 1 equiv) was refluxed for 24 h in HCl (30 mL, 1M, excess). The resulting solution was carefully neutralised with $NaHCO_{3(aq)}$ and concentrated under reduced pressure. To the resulting solid was added Ac_2O (1.0 mL, excess) and pyridine (0.7 mL excess) and stirred at room temperature for 24 h. The resulting solution was acidified with 1.0 M HCl to pH 4, then extracted with EtOAc (4 x 20 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5% EtOAc-petrol) to a complex mixture of inseparable compounds and pure **290A** (3 mg, 2%) as a colourless oil.

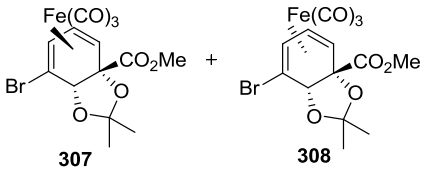
R_f = 0.70 (50% EtOAc-petrol); δ_H (500 MHz, $CDCl_3$) 5.91 (1H, d, *J* = 4.5 Hz), 5.56 (1H, s), 5.09 (1H, d, *J* = 10.0 Hz), 4.54 (1H, d, J_{AB} = 10.0 Hz), 4.29 (dd, *J* = 10.0, 4.5 Hz), 4.23 (1H, s), 3.97 (1H, d, J_{AB} = 10.0 Hz), 2.20 (3H, s), 2.15 (3H, s), 2.13 (3H, s), 1.99 (3H, s); δ_c (100 MHz, $CDCl_3$) 169.9 (C=O), 169.8 (C=O), 169.7 (C=O), 169.4 (C=O), 83.4 (CH(O)), 78.3 (CH(O)), 75.2 (CH(O)), 72.1 (CH(O)), 69.9 (CH(O)), 69.7 (CH(O)), 55.4(CH_2), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 20.5 (CH_3); HRMS (ESI+) m/z calcd for $(C_{15}H_{22}O_{11}+Na)^+$, 401.1055; found 401.0615.

9.4 Chapter 3: Bromo-diene Experimental

9.4.1 (4*S*)-tricarbonyl(*η*^{4}-(3a*S*,7a*S*)-methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate)iron(0)

and

9.4.2 (4*R*)-tricarbonyl(*η*^{4}-(3a*S*,7a*S*)-methyl 7-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate)iron(0)



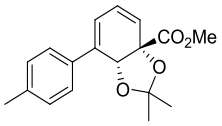
307 **308**

To a flask containing **304** (185 mg, 0.59 mmol, 1 equiv) in a glovebox was added nonacarbonyldiiron (440 mg, 1.21 mmol, 2 equiv). THF (40 mL) was added and the reaction mixture was stirred at room temperature for 7 d. The reaction mixture was then concentrated under reduced pressure (***Care! Toxic pentacarbonyliron distilled over at this point***) and purified by column chromatography (10% EtOAc-petrol) to give **307** as fine brown needles (43 mg, 17%) and **308** as a brown oil (36 mg, 14%). Unreacted **304** (100 mg, 60%) was also isolated. **307** was crystallized using EtOAc-petrol to obtain crystals suitable for X-Ray crystal structure analysis.

307: m.p 95-97 °C (EtOAc-petrol); R_f = 0.32 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -10 (*c* 0.20, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 5.95 (1H, dt, *J* = 4.5, 1.5 Hz, CBr=CH), 5.47 (1H, dd, *J* = 6.5, 4.5 Hz CBr=CH-C*H*=), 5.36 (1H, d, *J* = 1.5 Hz CH-O-), 3.88 (3H, s, O-CH_3), 3.06 (1H, dd, *J* = 6.5, 1.0 Hz CBr=CH-CH=C*H*), 1.45 (3H, s, C-CH_3), 1.23 (3H, s, C-CH_3); δ_c (75 MHz, $CDCl_3$) 171.3 (-*C*OOMe), 117.8 (-O-C-O-), 89.9 (CBr=*C*H), 87.0 (*C*-COOMe), 86.7 (CH-O-), 83.6 (CBr=CH-*C*H=), 70.2 (CBr), 54.0 (CBr=CH-CH=*C*H), 53.3 (O-CH_3), 28.1 (C-*C*H_3), 27.3 (*C*-CH_3); ν_{max} (film) 2981, 2068, 2003, 1730, 1437, 1375, 1261, 1214, 1162, 1062, 1027, 978, 865, 752, 687, 636 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{14}H_{13}BrFeO_7+Na)^+$, 450.9092, 452.9071; found 450.9106, 452.9164.

308: R_f = 0.26 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -90 (*c* 0.6, CH_2Cl_2); δ_H (500 MHz, $CDCl_3$) 5.76 (1H, d, *J* = 3.5 Hz, CBr=CH), 5.15 (1H, dd, *J* = 6.0, 4.5 Hz, CBr=CH - C*H*=), 4.60 (1H, s, CH-O-), 3.75 (3H, s, O-CH_3), 2.97 (1H, d, *J* = 6.5 Hz, CBr=CH-CH=C*H*), 1.71 (3H, s, C-CH_3), 1.20 (3H, s, C-CH_3); δ_c (75 MHz, $CDCl_3$) 207.1 (Fe C=O), 173.3 (-COOMe), 109.7 (-O-C-O-), 89.3 (CBr=*C*H), 85.4 (*C*-COOMe), 84.8 (CH-O-), 80.5 (CBr=CH-*C*H=), 73.6 (CBr), 61.2 (CBr=CH-CH=*C*H), 53.1 (O-CH_3), 25.0 (C-*C*H_3), 24.2 (C-*C*H_3); ν_{max} (film) 2980, 2061, 1995, 1729, 1460, 1380, 1252, 1207, 1168, 1070, 1030 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{14}H_{13}BrFeO_7+Na)^+$, 450.9092, 452.9071; found 450.9091, 452.9073.

9.4.3 (3a*S*,7a*R*)-methyl 2,2-dimethyl-7-(*p*-tolyl)-3a,7a-dihydrobenzo [d][1,3]dioxole-3a-carboxylate

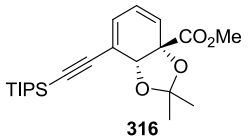


315

Bromodiene **304** (25 mg, 0.096 mmol, 1 equiv), tetrakis(triphenylphosphine)palladium (2 mg, 2 µmol, 2 mol %), *para*-tolylboronic acid (105 mg, 0.78 mmol, 8 equiv) and potassium carbonate (238 mg, 1.73 mmol, 18 equiv) were dissolved in DMF-H_2O 5:1 (30 mL) and stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). The organic layer was devoid of product; thus, the aqueous layer was concentrated under pressure to afford crude free acid cross-coupling product **314**. The crude acid **314** was then dissolved in MeOH-benzene 1:1 (35 mL) and (trimethylsilyl)diazomethane (1.5 mL, 2.0 M in hexane) was added dropwise with stirring until the yellow colour persisted and effervescence ceased. The solution was stirred for 2 h then concentrated under reduced pressure. Purification by column chromatography (10% EtOAc-petrol) to give **315** (8 mg, 30% over two steps) as a colourless oil:

R_f = 0.36 (5% EtOAc-petrol); $[\alpha]_D^{25}$ -156 (*c* 0.3, CH_2Cl_2); δ_H (250 MHz, $CDCl_3$) 7.50 (2H, d, *J* = 8.0 Hz, Ar-H), 7.18 (2H, d, *J* = 8.0 Hz, Ar-H) 6.48 (1H, d, *J* = 6.0 Hz, Ar-C=CH), 6.23 (1H, dd, *J* = 9.5, 6.0 Hz, Ar-C=CH-C*H*), 5.83 (1H, d, *J* = 9.5 Hz, Ar-C=CH-CH=C*H*), 5.26 (1H, s, CH-O-C), 3.77 (3H, s, O-CH_3), 2.36 (3H, s, Ar-CH_3), 1.53 (3H, s, C-CH_3), 1.42 (3H, s, C-CH_3); δ_c (75 MHz, $CDCl_3$) 171.8 (C=O), 138.2 , 135.3, 134.6, 129.4 , 125.8, 124.8 (Ar-C=CH-*C*H), 124.5 (Ar-C=CH-CH=*C*H), 119.7 (Ar-C=*C*H), 107.6 (-O-C-O-), 81.2 (*C*-COOMe), 74.6 (CH-O-), 53.1 (O-CH_3), 27.1 (C-*C*H_3), 25.4 (C-*C*H_3), 21.4 (Ar-CH_3); ν_{max} (film) 2973, 2937, 2888, 1741, 1469, 1381, 1308, 1163, 1131, 1105, 951, 821 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{18}H_{20}O_4+Na)^+$, 323.1259; found 323.1258.

9.4.4 (3a*S*,7a*R*)-methyl 2,2-dimethyl-7-((triisopropylsilyl)ethynyl)-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate

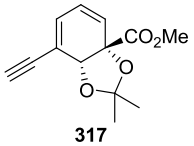


316

To a solution of bromodiene **304** (81 mg, 0.28 mmol, 1 equiv), tetrakis(triphenylphosphine)palladium (16 mg, 0.014 mmol, 5 mol %), copper(I) iodide (3.7 mg, 0.0196 mmol, 7 mol%) dissolved in THF (20 mL), was added by syringe *n*-butylamine (110 µL, 1.12 mmol, 4 equiv) and (tri*iso*-propyl)acetylene (100 µL, 0.45 mmol, 1.6 equiv). The reaction mixture was stirred at room temperature for 24 h, then diluted with EtOAc (20 mL) and washed with $NH_4Cl_{(aq)}$ (20 mL) and saturated brine (20 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% EtOAc-petrol) to give **316** (108 mg, 98%) as a yellow oil:

R_f = 0.45 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -176 (*c* 0.9, CH_2Cl_2); δ_H (250 MHz, $CDCl_3$) 6.37 (1H, d, *J* = 6.0 Hz, SiC≡C-C=C*H*), 6.12 (1H, dd, *J* = 9.5, 6.0 Hz, SiC≡C-C=CH-C*H*), 5.85 (1H, dd, *J* = 9.5, 0.5 Hz, SiC≡C-C=CH-CH=C*H*), 4.91 (1H, d, *J* = 0.5 Hz, CH-O-), 3.78 (3H, s, O-CH_3), 1.45 (3H, s, C-CH_3), 1.39 (3H, s, C-CH_3), 1.08 (21H, br s, Si-CH and Si-CH-CH_3); δ_c (75 MHz, $CDCl_3$) 171.7 (C=O), 129.0 (C=C), 125.0 (C=C), 124.4 (C=C), 120.7 (C=C), 108.2 (-O-C-O-), 105.5 (C≡C), 96.7 (C≡C), 80.0 (*C*-COOMe), 75.6 (CH-O-), 53.0 (O-CH_3), 26.9 (C-*C*H_3), 25.6 (C-*C*H_3), 18.6 (Si-C-*C*H_3), 11.3 (Si-*C*-CH_3); ν_{max} (film) 2943, 2865, 2158, 2032, 1741, 1462, 1381, 1243, 1039, 883, 677 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{22}H_{34}O_4Si+Na)^+$, 413.2124; found 413.2127.

9.4.5 (3a*S*,7a*R*)-methyl 7-ethynyl-2,2-dimethyl-3a,7a-dihydrobenzo [d][1,3]dioxole-3a-carboxylate

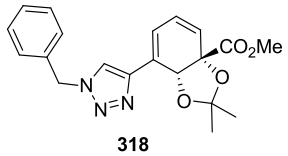


317

To a stirred solution of silylacetylene **316** (9.6 mg, 0.03 mmol, 1 equiv) in THF (30 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.05 mL, 0.05 mmol, 1.1 equiv). The reaction mixture was stirred for 24 h, then diluted with EtOAc (10 mL) and washed with saturated brine (10 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (15% EtOAc-petrol) to give **317** (4.4 mg, 0.015 mmol, 76%) as a pale white gum:

R_f = 0.24 (15% EtOAc-petrol); $[\alpha]_D^{25}$ -184 (*c* 0.34, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 6.46 (1H, d, *J* = 6.0 Hz, HC≡C-C=C*H*), 6.14 (1H, dd, *J* = 9.5, 6.0 Hz, HC≡C-C=CH-C*H*), 5.90 (1H, d, *J* = 9.5 Hz, HC≡C-C=CH-CH=C*H*), 4.92 (1H, s, CH-O-), 3.80 (3H, s, O-CH_3), 3.23 (1H, s, C≡CH), 1.48 (3H, s, C-CH_3), 1.43 (3H, s, C-CH_3); δ_c (75 MHz, $CDCl_3$) 171.5 (C=O), 130.6 (HC≡C-C=*C*H), 126.1 (HC≡C-C=CH-CH=*C*H), 123.8 (HC≡C-C=CH-*C*H), 118.8 (HC≡C-*C*=), 108.1 (-O-C-O-), 82.6 (HC≡*C*), 81.8 (H*C*≡C), 80.1 (*C*-COOMe), 75.0 (CH-O), 53.3 (O-CH_3), 27.0 (C-*C*H_3), 25.4 (C-*C*H_3); ν_{max} (film) 2981, 2889, 1737, 1462, 1382, 1251, 1152, 954, 807 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{13}H_{14}O_4+Na)^+$, 257.0784; found 257.0751.

9.4.6 (3a*S*,7a*R*)-methyl 7-(1-benzyl-1H-1,2,3-triazol-4-yl)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole-3a-carboxylate



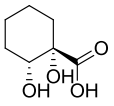
318

To a stirred solution of terminal alkyne **317** (13.0 mg, 0.05 mmol, 1 equiv) in EtOH-H_2O 5:1 (25 mL) were added benzyl azide (7.9 mg, 0.06 mmol, 1.2 equiv), $CuSO_4$ (1.1 mg, 1 mol %) and ascorbic acid (5.9 mg, 10 mol%). The solution was stirred at room temperature for 48 h, then diluted with saturated brine and extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% to 50% EtOAc-petrol) to give unreacted **317** (7.8 mg, 66%) and **318** (6.3 mg, 34%) as a pale brown oil:

R_f = 0.48 (50% EtOAc-petrol); $[\alpha]_D^{25}$ -40 (*c* 0.18, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.62 (1H, s, HetAr–H), 7.37 – 7.29 (5H, m, Ph–H) 6.94 (1H, d, *J* = 6.0 Hz, HetAr–C=CH–), 6.28 (1H, dd, *J* = 9.0, 6.0 Hz, HetAr–C=CH–C*H*=), 5.92 (1H, d, *J* = 9.0 Hz, HetAr–C=CH–CH=C*H*), 5.61 (1H, d, *J* = 15.0 Hz, Ph–C*H*H–), 5.49 (1H, d, *J* = 15.0 Hz, Ph–CH*H*–) 5.27 (1H, s, CH–O–), 3.78 (3H, s, O–CH_3), 1.48 (3H, s, C–CH_3), 1.34 (3H, s, C–CH_3); δ_c (75, $CDCl_3$ MHz) 172.0 (C=O), 134.8, 129.3, 128.8, 128.1, 127.8, 126.1, 124.9, 124.5, 121.0 (3º HetAr), 119.7 (HetAr–C=*C*H–), 108.7 (–O–C–O–), 80.6 (*C*–COOMe), 74.2 (CH–O–), 54.3 (Ph–CH_2–), 53.2 (O–CH_3), 27.1 (C–CH_3), 25.8 (C–CH_3); ν_{max} (film) 2995, 2917, 1857, 1739, 1496, 1457, 1258, 1066, 887, 799, 727 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{20}H_{21}N_3O_4+Na)^+$, 390.1429; found 390.1440.

9.5 Chapter 5: Peracid epoxidation experimental

9.5.1 (1*S*,2*R*)-1,2-dihydroxycyclohexanecarboxylic acid



383

A stirred solution of **30** (65 mg, 0.33 mmol) and Pd/C (10 mg, 10 wt. % loading, matrix activated carbon support) in MeOH (20 mL) was exposed to a hydrogen atmosphere at room temperature. After 24 h the solution was filtered and washed through a plug of celite and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (60% EtOAc 35% petrol 2.5% H_2O 2.5% AcOH) to yield pure **383** (20mg, 38%) as a white crystalline solid.

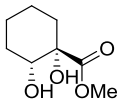
Or

A stirred solution of **206** (857 mg, 5.48 mmol) and Pd/C (50 mg, 10 wt. % loading, matrix activated carbon support) in MeOH (20 mL) was exposed to a hydrogen atmosphere at room temperature. After 24 h the solution was filtered and washed through a plug of celite and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (60% EtOAc 35% petrol 2.5% H_2O 2.5% AcOH) to yield pure **383** (625mg, 71%) as a white crystalline solid.

383 has been reported previously; spectroscopic data are in agreement with published values.[208,209]

m.p = 112-115 °C (EtOAc:petrol); R_f = 0.10 (60% EtOAc 35% petrol, 2.5% H_2O, 2.5% AcOH); $[\alpha]_D^{25}$ + 13.3 (*c* 0.3, H_2O); δ_H (300 MHz, D_2O) 3.76 (1H, dd, *J* = 11.5, 3.5 Hz, C*H*(OH)), 1.60 – 1.56 (4H, m, CH), 1.40 – 1.08 (4H, m, CH); δ_c (125 MHz, MeOD) 180.1 (C=O), 79.5 (*C*(OH)CO_2H), 73.7 (CH(OH)), 35.0, 30.8, 25.3, 21.1 (CH_2); ν_{max} (film) 3445, 3086, 2924, 2858, 1736, 1439, 1199, 1138, 1023, 948, 821 cm^{-1}; HRMS (ESI-) m/z calcd for $(C_7H_{12}O_4\text{-}H)^-$, 159.0657; found 159.0672.

9.5.2 (1*S*,2*R*)-methyl 1,2-dihydroxycyclohexanecarboxylate



387

To a stirred solution of **383** (47 mg, 0.29 mmol) dissolved in MeOH:C_6H_6 (6 mL 1:1 ratio), was added TMS-CHN_2 (0.2 mL, 2.0 M solution in THF, 0.4 mmol, 1.4 equiv) until a yellow colour persisted. Solvent was removed under reduced pressure [CAUTION - TMS-CHN_2 diazomethane extremely toxic, removed under reduced pressure in fume hood, with acetic acid in solvent trap to quench any unreacted reagent] Pure **387** was obtained (52 mg, 100%) as a yellow oil.

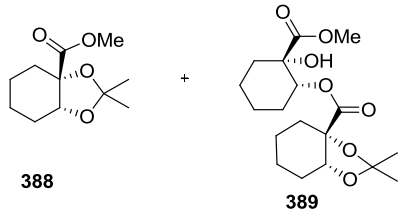
387 has been reported previously; spectroscopic data are in agreement with published values.[211,212]

R_f = 0.05 (30% EtOAc-petrol); $[\alpha]_D$ -10.0 (*c* 0.3, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 3.82 – 3.74 (1H, m, CH(OH)), 3.77 (3H, s, CH_3), 2.86 (2H, br s, OH), 1.83 – 1.22 (8H, m, CH); δ_c (75 MHz, $CDCl_3$) 176.3 (C=O), 76.8 (*C*(OH)(CO_2CH_3)), 72.2 (*C*H(OH)), 52.9 (OCH_3), 34.2 (CH_2), 30.0 (CH_2), 23.9 (CH_2), 19.7 (CH_2); ν_{max} (film) 3453, 2938, 2861, 1729, 1438, 1272, 1238, 1207, 1149, 1079, 998, 923 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_8H_{14}O_4+H)^+$, 175.0970; found 175.0981.

9.5.3 (3a*S*,7a*R*)-methyl 2,2-dimethylhexahydrobenzo[d][1,3] dioxole-3a-carboxylate

and

9.5.4 (3a*S*,7a*R*)-(1*R*,2*S*)-2-hydroxy-2-methoxycarbonyl)cyclohexyl 2,2-dimethylhexahydrobenzo[d][1,3]dioxole-3a-carboxylate



388 **389**

To a stirred solution of **387** (53 mg, 0.30 mmol) dissolved in acetone (10 mL, freshly distilled), was added 2,2-Dimethoxypropane (0.45 mL, 3.65 mmol, 12 equiv) and *para*-toluenesulfonic acid (6 mg, 0.03 mmol, 10 mol %). The solution was stirred at room temperature under N_2 for 20 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0-20% EtOAc-petrol) to yield **388** a colourless oil (40 mg, 61%).

R_f = 0.70 (30% EtOAc-petrol); $[\alpha]_D^{25}$ -37.8 (*c* 0.65, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.35 (1H, t, *J* = 3.5 Hz, *C*H(OC(CH_3)$_2$), 3.75 (3H, s, OCH_3), 2.06 – 1.93 (2H, m, C-H), 1.50 (3H, d, *J* = 0.5 Hz, CH_3) 1.35 (3H, d, *J* = 0.5 Hz, CH_3), 1.85 – 1.23 (6H, m, C-H); δ_c (75 MHz, $CDCl_3$) 173.2 (C=O), 108.9 (*C*(CH_3)$_2$), 81.0 *C*(OC(CH_3)$_2$)(CO_2CH_3), 74.9 (*C*H(OC(CH_3)$_2$), 52.5 (OCH_3), 32.3, 28.0, 25.9, 25.8, 20.5, 18.7; ν_{max} (film) 2997, 2941, 2873, 1733, 1450, 1383, 1217, 1160, 1054, 1025, 905, 725 cm^{-1}; HRMS (ESI+) m/z calcd for ($C_{11}H_{17}NaO_4$+H)$^+$, 237.1102; found 237.1079.

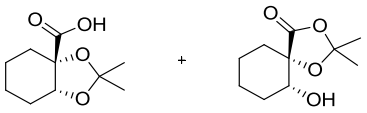
On repeating this previous experimental procedure, small amounts. (20 mg, 2%) of byproduct **389** were isolated:

R_f = 0.85 (50% EtOAc-petrol); $[\alpha]_D^{25}$ -21 (*c* 1.6, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 5.08 (1H, dd, *J* = 10.0, 6.0 Hz, CH(OC=O)), 4.26 (1H, t, *J* = 3.2 Hz, CH(O)), 3.73 (3H, s, OCH_3), 3.24 (1H, s, OH), 2.06 – 1.24 (16H, m, CH), 1.50 (3H, s, CH_3), 1.35 (3H, s, CH_3); δ_c (125 MHz, $CDCl_3$) 175.3 (CO_2CH_3), 171.8 (C=O), 108.9 ($C(CH_3)_3$), 80.7, 75.6, 75.3, 74.9, 53.0 (OCH_3), 34.1, 32.2, 27.7, 26.1, 25.7, 25.6, 23.6, 20.2, 19.6, 18.3; ν_{max} (film) 3523, 2987, 2938, 2865, 1733, 1449, 1381, 1370, 1243, 1216, 1152, 1124, 1046, 1003, 874, 735 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{18}H_{28}O_7+H)^+$, 357.1908; found 357.1929.

9.5.5 (3a*S*,7a*R*)-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-3a-carboxylic acid

and

9.5.6 (5*S*,6*R*)-6-hydroxy-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-4-one



384 **390**

388 (253 mg, 1.18 mmol) was dissolved in THF (10 mL) and NaOH (6 mL, 2M in H_2O, 12 mmol, 10 equiv) and refluxed overnight. The resulting solution washed with EtOAc (3 x 10 mL) to remove any unreacted starting material, the remaining aqueous layer was acidified to pH 2.0 and extracted with EtOAC (3 x 10 mL) and combined organic layers were washed with saturated brine and dried over $MgSO_4$. The resulting oil was purified via flash column chromatography (50% EtOAc-petrol) to yield three compounds, acetonide migration product **390** (30 mg, 13%), acid **384** (20 mg, 8%) and diol acid **383** (40 mg, 21%).

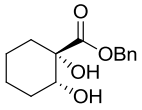
Or

A stirred solution of benzyl ester **393** (32 mg, 0.11 mmol) and Pd/C (10 mg, 10 wt. % loading, matrix activated carbon support) in MeOH (20 mL) was exposed to a hydrogen atmosphere at room temperature. After 24 h the solution was filtered through a plug of celite and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0-50 % EtOAc-petrol) to yield pure **384** (14 mg, 63 %) as a colourless oil.

384: R_f = 0.40 (50% EtOAc-petrol); $[\alpha]_D^{25}$ -40.0 (*c* 0.70, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.31 (1H, t, *J* = 3.5 Hz, *C*H($OC(CH_3)_2$), 2.12-1.97 (2H, m, C-H), 1.90-1.78 (1H, m, C-H), 1.54 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.71-1.51 (4H, m, C-H), 1.28-1.21 (1H, m, C-H); δ_c (75 MHz, $CDCl_3$) 175.6 (C=O), 109.6 (*C*(CH_3)$_2$), 80.7 *C*($OC(CH_3)_2$)(CO_2H), 74.9 (*C*H($OC(CH_3)_2$), 32.3, 27.9, 25.9, 25.6, 20.7, 18.5; ν_{max} (film) 2994, 2939, 2873, 2714, 1450, 1371, 1383, 1217, 1174, 905, 725 cm^{-1}; HRMS (ESI-) m/z calcd for $(C_{10}H_{16}O_4)^-$, 199.0970; found 199.0975.

390 rearrangement: R_f = 0.83 (50% EtOAc-petrol); $[\alpha]_D^{25}$ +2.0 (*c* 1.5, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 3.75 (1H, dd, *J* = 11.5, 4.6 Hz, CH(OH)), 1.95 – 1.93 (1H, m, CH), 1.92-1.89 (1H, m, CH), 1.88 (1H, brs, OH), 1.77-1.80 (1H, m, CH), 1.73 (1H, td, *J* = 14.0, 4.5 Hz, CH), 1.66 (3H, s, CH_3), 1.63 (1H, m, CH), 1.63 (3H, s, CH_3), 1.49 – 1.55 (1H, m, CH), 1.44 – 1.48 (1H, m, CH), 1.38 (1H, tt, *J* = 13.0, 3.5 Hz, CH); δ_c (125 MHz, $CDCl_3$) 174.0 (C=O), 110.1 (*C*$(CH_3)_3$), 83.2 (*C*(O)(C=O), 70.9 (C(OH)H), 33.6 (CH_2), 30.6 (CH_2), 29.0 (C(*C*$H_3)_3$), 27.9 (C(*C*$H_3)_3$), 23.6 (CH_2), 20.1 (CH_2); ν_{max} (film) 3484, 2991, 2939, 2863, 2774, 1448, 1385, 1291, 1262, 1060, 1036, 908, 860, 626 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{10}H_{16}O_4+H)^+$, 201.1127; found 201.1113.

9.5.7 (1*S*,2*R*)-benzyl 1,2-dihydroxycyclohexanecarboxylate

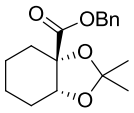


392

To a stirred solution of **383** (43 mg, 0.26 mmol) and triethylamine (0.10 mL, 0.91 mmol, 3.4 equiv) dissolved in CH_2Cl_2 (10 mL), was added Benzyl Bromide (0.12 mL, 0.91 mmol, 3.4 equiv). Solution was stirred for 3 h. The resulting solution was washed with water (10 mL) then the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10-50% EtOAc-petrol) to yield **392** a colourless oil (28 mg, 42%).

R_f = 0.10 (30% EtOAc-petrol); $[\alpha]_D^{25}$ -2.35 (*c* 0.4, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 7.36 (5H, s, Ar-H), 5.27 (1H, d, J_{AB} = 12.0 Hz, CH_2), 5.21 (1H, d, J_{AB} = 12.0 Hz, CH_2), 3.86 (1H, dd, *J* = 11.3, 4.5, C*H*(OH)), 1.88 – 1.20 (8H, m, CH); δ_c (75 MHz, $CDCl_3$) 176.0 (C=O), 125.3, 128.6, 128.4, 127.9 (Ar-C), 76.8 (C), 72.2 (C(OH), 67.6 (OCH_2Bn), 34.2 (CH_2), 30.2 (CH_2), 23.9 (CH_2), 17.8 (CH_2); ν_{max} (film) 3465, 2937, 2860, 1728, 1498, 1449, 1232, 1148, 1066, 951, 909, 735 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{14}H_{17}O_4+H)^+$, 251.1283; found 251.1267.

9.5.8 (3a*S*,7a*R*)-benzyl 2,2-dimethylhexahydrobenzo[d][1,3] dioxole-3a-carboxylate

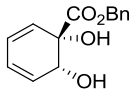


393

To a stirred solution of **392** (28 mg, 0.11 mmol) dissolved in acetone (10 mL, freshly distilled), was added 2,2-Dimethoxypropane (0.16 mL, 1.34 mmol, 12 equiv) and *para*-toluenesulfonic acid (2 mg, 0.01 mmol, 10 mol %). The solution was stirred at room temperature under N_2 for 20 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure to obtain **393** (30 mg, 92%) as a colourless oil. Material was taken forward unpurified.

R_f = 0.75 (30% EtOAc-petrol); $[\alpha]_D^{25}$ –23.3 (*c* 1.25, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.36-7.33 (5H, m, Ar-H), 5.21 (2H, s, CH_2), 4.38 (1H, t, *J* = 3.5 Hz, CH(O)), 2.05-1.97 (2H, m, CH), 1.83-1.25 (6H, m, CH), 1.52 (3H, s, CH_3), 1.36 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 172.7 (C=O), 135.7, 128.7, 128.4, 128.2 (Ar-C), 109.1 ($C(CH_3)_2$), 81.0 $C(OC(CH_3)_2)(CO_2Bn)$, 75.1 ($CH(OC(CH_3)_2)$, 66.9 (CH_2), 32.2, 28.0, 25.9, 25.8, 20.3, 18.6; ν_{max} (film) 2994, 2935, 2865, 1731, 1498, 1455, 1337, 1244, 1215, 1021, 998, 874, 742, 696 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{17}H_{24}O_4+H)^+$, 291.1591; found 291.1574.

9.5.9 (1*S*,6*R*)-benzyl 1,6-dihydroxycyclohexa-2,4-dienecarboxylate

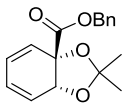


394

Benzyl bromide (0.93 mL, 7.83 mmol, 1.1 equiv) was dissolved in acetone (50 mL) containing triethylamine (1.10 mL, 7.83 mmol, 1.1 equiv) to which was added dropwise a solution of microbial diol acid **30** (1.12 g, 7.12 mmol, 1 equiv) in acetone (50 mL). The resulting solution was stirred for 4 h. The resulting solution was diluted with EtOAc (50 mL), and extracted with LiCl (2 × 15 mL). The organic layer was dried over $MgSO_4$ to yield pure **394**, a colourless oil. (1.10 g, 61%).

R_f = 0.29 (40% EtOAc-petrol); $[\alpha]_D^{25}$ -135.6 (*c* 1.6, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$); 7.36 (5H, br.s, Bn), 6.13 (1H, dddd, *J* 9.5, 4.0, 1.0, 0.5 Hz C=CH), 5.94 (1H, dddd, *J* 9.5, 5.0, 2.5, 0.5 Hz, C=CH), 5.82 (1H, ddd, *J* 9.5, 2.0, 1.0 Hz, C=CH), 5.76 (1H, ddd, *J* 9.5, 2.0, 1.0 Hz, C=CH), 5.29 (1H, s, CO_2-CH_2-Ar), 4.87 (1H, m, C(O)H); δ_C (75 MHz, $CDCl_3$); 175.0 (C=O), 134.9 (Ar), 131.9 (C=C), 128.7, 128.6, 128.1, (Ar) 126.8, 124.6, 122.7 (C=C), 74.0 (*C*(OH)C=O) , 70.9 (C(OH)-H), 68.3 (O-CH_2); ν_{max} (film) 3451, 3038, 1731, 1660, 1455, 1378, 1234, 1168, 1077, 1020, 909, 753, 695 cm^{-1}; HRMS (+ve ESI-TOF) m/z calculated for $(C_{14}H_{14}O_4+Na)^+$, 269.0789; found 269.0863.

9.5.10(3a*S*,7a*R*)-benzyl 2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3] dioxole-3a-carboxylate



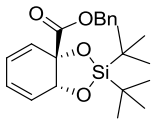
395

To a stirred solution of **394** (335 mg, 1.37 mmol) dissolved in acetone (10 mL, freshly distilled), was added 2,2-Dimethoxypropane (2.0 mL, 16.46 mmol, 12 equiv) and *para*-toluenesulfonic acid (26 mg, 0.03 mmol, 10 mol %). The solution was stirred for 20 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10-20% EtOAc-petrol) to yield **395** a colourless oil (358 mg, 92%).

395 has been reported previously; spectroscopic data are in agreement with published values.[76]

R_f = 0.60 (30% EtOAc-petrol); δ_H (250 MHz, $CDCl_3$) 7.28 – 7.25 (5H, m, Ar-H), 6.08 – 5.94 (3H, m, C=CH), 5.86 – 5.79 (1H, m, C=CH), 5.18 (2H, s, CH_2), 4.97 (1H, d, *J* = 4.0 Hz, CH(O)), 1.38 (3H, s, CH_3), 1.37 (3H, s, CH_3).

9.5.11(3a*S*,7a*R*)-benzyl 2,2-di-*tert*-butyl-3a,7a-dihydrobenzo[d][1,3,2]dioxasilole-3a-carboxylate

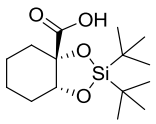


396

To a stirred solution of **394** (48 mg, 0.195 mmol) dissolved in CH_2Cl_2 (2 mL) was added triethylamine (60 µL, 0.46 mmol, 2.4 equiv) and *tert*-Butyldimethylsilyl trifluoromethanesulfonate (70 µL, 0.21 mmol, 1.1 equiv). The solution was stirred at room temperature for 9 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0-5% EtOAc-petrol) to yield **396** a colourless oil (61 mg, 81%).

R_f = 0.65 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -327.0 (*c* 3.31, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.35 – 7.31 (5H, m, Ar-H), 6.03 – 5.94 (3H, m, C=CH), 5.75 – 5.71 (1H, m, C=CH), 5.25 (1H, d, *J* = 12.0 Hz, H_{AB}), 5.18 (1H, d, *J* = 12.0 Hz, H_{AB}), 4.97 (1H, d, *J* = 1.8 Hz, CH(OSi)), 0.99 (9H, s, CH_3) 0.98 (9H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 172.2 (C=O), 135.5, 128.6, 128.4, 128.3, 126.3, 125.8, 123.8, 122.3, 78.6 (*C*(OSi)(C=O)), 71.5 (*C*H(OSi), 67.3 (CH_2), 27.0 (CH_3), 26.9 (CH_3), 21.1 ($C(CH_3)_3$), 20.2 ($C(CH_3)_3$); ν_{max} (film) 3045, 2966, 2934, 2891, 2859, 1733, 1473, 1229, 1091, 1031, 1012, 1000, 875, 825, 696 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{22}H_{30}O_4Si+H)^+$, 387.1991; found 387.1993.

9.5.12(3a*S*,7a*R*)-2,2-di-*tert*-butylhexahydrobenzo[d][1,3,2] dioxasilole-3a-carboxylic acid

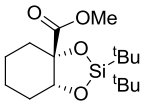


385

A stirred solution of **396** (61 mg, 0.16 mmol) and Pd/C (10 mg, 10 wt. % loading, matrix activated carbon support) in MeOH (20 mL) was exposed to a hydrogen atmosphere at room temperature. After 24 h the solution was filtered through a plug of celite and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10-70% EtOAc-petrol) to yield pure **385** (25 mg, 53%) as a colourless oil.

R_f = 0.30 (30% EtOAc-petrol); $[\alpha]_D^{25}$ -17.0 (*c* 0.18, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.36 (1H, dd, *J* = 11.0, 4.5 Hz, CH(OSi)), 1.99 – 1.20 (8H, m, CH), 1.02 (9H, s, CH_3), 0.98 (9H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 179.1 (C=O), 77.9 ((*C*(OSi)(C=O)), 73.9 (*C*H(OSi), 33.0 (CH_2), 30.1 (CH_2), 27.7 (CH_3), 27.5 (CH_3), 23.6, 20.5, 20.3, 19.6; ν_{max} (film) 3070, 2935, 2894, 2859, 1717, 1448, 1472, 1094, 827 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{15}H_{28}O_4Si+H)^+$, 301.1830; found 301.1830.

9.5.13(3a*S*,7a*R*)-methyl 2,2-di-*tert*-butylhexahydrobenzo[d][1,3,2] dioxasilole-3a-carboxylate



397

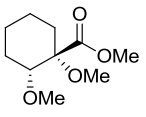
To a stirred solution of **387** (25 mg, 0.15 mmol) dissolved in CH_2Cl_2 (5 mL) was added triethylamine (50 µL, 0.34 mmol, 2.4 equiv) and *tert*-Butyldimethylsilyl trifluoromethanesulfonate (50 µL, 0.16 mmol, 1.1 equiv). The solution was stirred at room temperature under N_2 for 9 h. The resulting solution was diluted with EtOAc (10mL) followed by the addition of water (20mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0-5% EtOAc-petrol) to yield **397** a colourless oil (37 mg, 82%).

R_f = 0.50 (50% EtOAc-petrol); $[\alpha]_D^{25}$ -27.0 (*c* 0.14, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 4.26 (1H, dd, *J* = 9.0, 4.0 Hz), 3.74 (3H, s), 1.95-1.16 (8H, m), 0.99 (9H, s), 0.95 (9H, s); δ_c (75 MHz, $CDCl_3$) 176.8 (C=O), 77.6, 74.5, 52.5, 33.4, 30.1, 27.5, 27.4, 23.8, 20.5, 20.3, 19.6; ν_{max} (film) 2934, 2892, 2858, 1731, 1472, 1438,1278, 1092, 768 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{16}H_{30}O_4Si+H)^+$, 315.1987; found 315.2045.

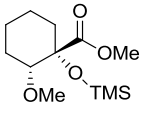
9.5.14(1*S*,2*R*)-methyl 1,2-dimethoxycyclohexanecarboxylate

and

(1*S*,2*R*)-methyl 2-methoxy-1-((trimethylsilyl)oxy) cyclohexanecarboxylate



399



401

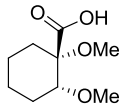
383 (133 mg, 0.83 mmol) dissolved in DMF (1 mL), was added dropwise to a suspension of NaH (109 mg, 2.74 mmols, 3.3 equiv of 60 % in mineral oil) in DMF (2 mL) at -22 °C. MeI (0.17 mL, 2.83 mmols, 3.4 mmols) was dropwise over 5 mins. The resulting solution was stirred at -22 °C and allowed to warm to room temperature over 19 h. The solution was cooled to -22 °C, $NH_4Cl_{(aq)}$ (10 mL) was added to the solution dropwise, then transferred into a separating funnel. EtOAc (20 mL) was added to the solution and the organic layers washed (3 × 10 mL) $LiCl_{(aq)}$,, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5-20% EtOAc-petrol) to yield a mixture of two products **399** and **400** as a colorless oil (99 mg).

The inseparable mixture was dissolved in CH_2Cl_2 (3 mL), addition of triethylamine (40 µL, 0.32 mmol) followed by Trimethylsilyl trifluoromethanesulfonate (50 µL, 0.29 mmol) stirred at room temperature for 30 h. The resulting mixture was diluted with EtOAc (20 mL) and washed with saturated brine (20 mL) dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (1-20% EtOAc-petrol) to yield a mixture of two purified products **401** (20 mg, 18%) **399** (40 mg, 42%).

401: R_f = 0.85 (20% EtOAc-petrol); $[\alpha]_D^{25}$ -1.4 (*c* 0.73, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 3.73 (3H, s, CO_2CH_3), 3.47 (1H, dd, *J* = 11.0, 4.5 Hz, CH(OC*H*$_3$)), 3.29 (3H, s, OCH_3), 1.85-0.84 (8H, m, CH), 0.15 (9H, s, $Si(CH_3)_3$); δ_c (75 MHz, $CDCl_3$) 175.6 (C=O), 82.2, 76.1, 56.7, 51.8, 36.2, 25.1, 24.0, 20.3, 2.2; ν_{max} (film) 2949, 2860, 1753, 1446, 1366, 1279, 1244, 1156, 1062, 1041, 837, 760, 734 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{12}H_{24}O_4Si+H)^+$, 261.1522; found 261.1515.

399: R_f = 0.20 (20 % EtOAc-petrol); $[\alpha]_D^{25}$ -26.9 (c 2.23, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 3.73 (3H, s, CO_2CH_3), 3.44 (1H, dd, *J* = 11.0, 4.0 Hz, C*H*(OCH_3)), 3.36 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 2.04-0.80 (8H, m, CH); δ_c (75 MHz, $CDCl_3$) 174.1 (C=O), 82.9, 81.7, 57.0, 52.1, 51.8, 29.6, 24.7, 23.6, 20.3; ν_{max} (film) 2938, 2861, 1730, 1446, 1373, 1275, 1227, 1099, 1061, 997 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{10}H_{18}O_4+H)^+$, 203.1283; found 203.1289.

9.5.15(1*S*,2*R*)-1,2-dimethoxycyclohexanecarboxylic acid



403

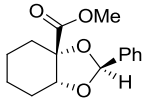
399 (67 mg, 0.33 mmol) was dissolved in THF (1.0 mL) and NaOH (1.0 mL, 2M in H_2O, 20 µmol, 60 equiv) and refluxed overnight. The resulting solution extracted with EtOAC (3 x 10 mL) to remove any unreacted starting material, the remaining aqueous layer was acidified to pH 2.0 and extracted with EtOAC (3 × 10 mL), combined organic layers washed with saturated brine and dried over $MgSO_4$. The resulting oil was purified via flash column chromatography (50% EtOAc, 45% petrol, 2.5% AcOH, 2.5% H_2O) to yield **403** a colorless oil (22 mg, 35%).

R_f = 0.25 (50% EtOAc, 45% petrol, 2.5 % AcOH, 2.5% H_2O); $[\alpha]_D^{25}$ -20.5 (*c* 0.73, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 3.40-3.37 (1H, m, C*H*(OCH_3)), 3.38 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 2.18 (1H, dd, *J* = 15.0, 2.0 Hz, CH), 1.96 (1H, m, CH), 1.82-1.81 (1H, m, CH), 1.68-1.53 (3H, m, CH), 1.37-1.25 (2H, m, CH); δ_c (125 MHz, $CDCl_3$) 175.3 (C=O), 82.7, 81.2, 57.1, 52.0, 28.1, 24.8, 23.7, 20.0; ν_{max} (film) 3143, 2940, 2860, 2838, 1721, 1464, 1448, 1308, 1196, 1099, 1077, 973, 939 cm^{-1}; HRMS (ESI-) m/z calcd for $(C_9H_{16}O_4\text{-}H)^-$, 187.0970; found 187.0972.

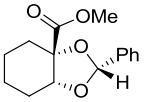
9.5.16(2*S*,3a*S*,7a*R*)-methyl 2-phenylhexahydrobenzo[d] [1,3] dioxole-3a-carboxylate

and

9.5.17(2*R*,3a*S*,7a*R*)-methyl 2-phenylhexahydrobenzo[d][1,3] dioxole-3a-carboxylate



408



409

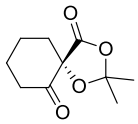
387 (30 mg, 0.27 mmol) dissolved in toluene (15 mL). Benzaldehyde (0.03 mL, 0.34 mmol, 2 equiv) and *para*-toluenesulfonic acid (4 mg, 0.02 mmol, 10 mol%) was added. The resulting solution was refluxed for 24 h and monitored by TLC. The resulting cooled solution was quenched with $NaHCO_3$ (15 mL) and extracted with EtOAC (3 × 10 mL). Combined organic layers were dried over $MgSO_4$. The resulting oil was purified via flash column chromatography (5-10% EtOAc-petrol) to yield both diastereoisomers **408** (10 mg, 24%) **408** + **409** (17 mg, 40%), **409** (15 mg, 35%). Overall 99% yield.

408: R_f = 0.53 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -1.6 (*c* 0.08, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.49-7.45 (2H, d, *J* = 7.6 Hz, Ar-H), 7.39-7.32 (3H, m, Ar-H), 6.21 (1H, s, CH(O)(O)), 4.53 (1H, t, *J* = 5.5 Hz, CH(O)), 3.70 (3H, s, OCH_3), 2.03-1.89 (4H, m, CH), 1.75 – 1.39 (4H, m, CH); δ_c (75 MHz, $CDCl_3$) 173.0 (C=O), 138.9, 129.0, 128.3, 126.4 (Ar-C), 102.8 (CH(O)(O)(Ar)), 81.9 (*C*(O)(C=O)), 75.9 (C(O)H), 52.3 (OCH_3), 30.6, 26.1, 20.8, 20.4; ν_{max} (film) 2938, 2863, 1735, 1451, 1247, 1162, 1093, 698 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{15}H_{18}O_4+H)^+$, 263.1283; found 263.1268.

409: R_f = 0.49 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -31 (*c* 0.7, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.56 – 7.52 (2H, m, Ar-H), 7.40 – 7.37 (3H, m, Ar-H), 5.97 (1H, s, CH(O)(O)), 4.41 (1H, t, *J* = 4.0 Hz, CH(O)), 3.82 (3H, s, OCH_3), 2.13 – 1.81 (4H, m, CH), 1.76 – 1.45 (4H, m, CH); δ_c (75 MHz, $CDCl_3$) 173.4 (C=O), 137.2, 129.3, 128.3, 126.6 (Ar-C), 103.2 (CH(O)(O)(Ar)), 81.4 (*C*(O)(C=O)), 77.3 (C(O)H), 52.5 (OCH_3), 31.1, 26.1, 19.4, 18.5; ν_{max} (film) 2951, 2869, 1734, 1451, 1247, 1163, 1088, 1024, 697 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{15}H_{18}O_4+H)^+$, 263.1283; found 263.1267.

9.6 Chapter 6: Shi like catalysts experimental

9.6.1 (*S*)-2,2-dimethyl-1,3-dioxaspiro[4.5]decane-4,6-dione



422

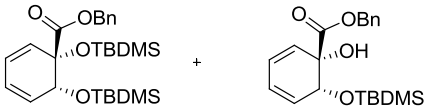
A stirred solution of **390** (25 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) was added Dess Martin Periodinane (131 mg, 0.31 mmol, 2.5 equiv). The resulting solution was heated to reflux for 24 h. To the cooled solution was added $NaHCO_{3(aq)}$ (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (0-20% EtOAc-petrol) to yield **422** a colourless oil (15 mg, 60%).

R_f = 0.25 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -50.0 (*c* 2.2, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 2.81 (1H, ddd, *J* = 13.9, 10.9, 5.5 Hz), 2.63 (1H, ddd, *J* = 13.9, 10.9, 5.5 Hz), 2.32-2.17 (2H, m), 2.08 – 1.97 (2H, m), 1.86 –1.73 (2H, m), 1.62 (3H, s, CH_3), 1.57 (3H, s, CH_3); δ_c (125 MHz, $CDCl_3$) 203.1 (C=O), 169.3 (C=O), 111.4 ($C(CH_3)_2$), 85.2, 39.5, 38.7, 28.4, 27.5, 26.5, 21.0; ν_{max} (film) 2996, 2941, 2921, 2872, 2851, 1784, 1732, 1394, 1380, 1283, 1254, 1130, 1077, 1045, 930 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{10}H_{14}O_4+Na)^+$, 221.0789; found 221.0787.

9.6.2 (1*S*,6*R*)-benzyl 1,6-bis((*tert*-butyldimethylsilyl)oxy) cyclohexa-2,4-dienecarboxylate

and

9.6.3 (1*S*,6*R*)-benzyl 1,6-bis((*tert*-butyldimethylsilyl)oxy) cyclohexa-2,4-dienecarboxylate



423 **424**

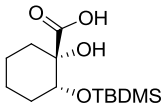
To a stirred solution of **394** (170 mg, 0.69 mmol) dissolved in CH_2Cl_2 (10 mL) was added triethylamine (0.07 mL, 0.47 mmol, 1.1 equiv) and *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.17 mL, 0.76 mmol, 1.1 equiv). The solution was stirred at room temperature for 4 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (1-10% EtOAc-petrol) to yield a colourless oil **423** (68 mg, 21%), **424** (195 mg, 78%).

423: R_f = 0.80 (10% EtOAc-petrol); $[\alpha]_D^{25}$ +41.4 (*c* 2.1, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38 – 7.32 (5H, m, Ar-H), 6.02 (1H, ddd, *J* = 9.5, 4.5, 1.0 Hz), 5.88 – 5.82 (1H, m, C=CH), 5.79-5.75 (2H, m, C=CH), 5.22 (1H, d, J_{AB} = 12.0 Hz), 5.13 (1H, d, J_{AB} = 12.0 Hz), 5.08 (1H, m), 0.88 (9H, s, CH_3), 0.82 (9H, s, CH_3), 0.08 (9H, s, CH_3), 0.01 (9H, s, CH_3), -0.01 (3H, s, CH_3), -0.02 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 174.3 (C=O), 135.5 (Ar-C), 135.2 (C=C), 128.6, 128.5, 128.3 (Ar-C), 127.0, 125.9, 121.6 (C=C), 77.7 (COSi), 73.8 (CH(OSi)), 67.3 (CH_2), 25.7, 25.7 (SiC(CH_3)$_3$), 18.7, 17.9 (SiC(CH_3)$_3$), -3.0, -3.1, -4.4, -4.9 ($SiCH_3$); ν_{max} (film) 2954, 2929, 2893, 2856, 1752, 1462, 1361, 1250, 1138, 1058, 905, 836, 777, 696 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{26}H_{42}O_4Si_2+Na)^+$, 497.2515; found 497.2580.

424: R_f = 0.45 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -84.6 (*c* 6.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.39 – 7.32 (5H, m, Ar-H), 6.12 (1H, dd, *J* = 9.5, 5.5 Hz), 5.92 (1H, dddd, *J* = 9.8, 5.5,

2.5, 1.0 Hz), 5.80 (1H, dd, *J* = 9.5, 1.0 Hz), 5.69 (1H, dt, *J* = 9.8, 1.0 Hz), 5.28 (1H, d, *J* = 12.0 Hz, H_{AB}), 5.15 (1H, d, *J* = 12.0 Hz, H_{AB}), 5.00 (1H, t, *J* = 2.5 Hz), 0.88 (9H, s, CH_3), 0.09 (3H, s, CH_3), -0.01 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 174.5 (C=O), 135.1 (Ar-C), 131.7 (C=C), 128.6, 128.4, 128.3 (Ar-C), 126.5, 124.7, 122.5 (C=C), 74.5 (COH), 72.5 (CH(OSi)), 67.6 (CH_2), 25.6 (SiC(CH_3)$_3$), 17.8 (SiC(CH_3)$_3$), -4.4, -5.3 ($SiCH_3$); ν_{max} (film) 3546, 3050, 2954, 2929, 2886, 1737, 1498, 1408, 1250, 1106, 1044, 1026, 939, 886, 777 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{20}H_{28}O_4Si+Na)^+$, 383.1650; found 383.1691.

9.6.4 (1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclo hexanecarboxylic acid



425

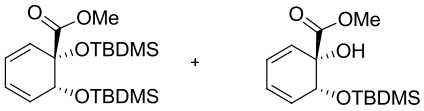
A stirred solution of **424** (177 mg, 0.49 mmol) and Pd/C (20 mg, 10 wt.% loading, matrix activated carbon support) in MeOH (20 mL) was exposed to a hydrogen atmosphere. After 24 h the solution was filtered through a plug of celite and concentrated under reduced pressure. The resulting oil was pure **425** (136 mg, 99%) as a colourless oil.

R_f = 0.20 (50 % EtOAc-petrol); $[\alpha]_D^{25}$ -19.5 (*c* 4.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.05 (1H, dd, *J* = 11.0, 4.5 Hz), 1.91 (1H, dq, *J* = 14.0, 3.0 Hz), 1.78-1.67 (3H, m), 1.58-1.45 (3H, m), 1.37-1.21 (3H, m), 0.84 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); δ_c (75 MHz, $CDCl_3$) 179.4 (C=O), 77.8 (C(OH)), 73.9 (CH(OSi)), 32.8, 30.3 (CH), 25.6 ($SiC(CH_3)_3$), 23.6, 19.5 (CH_2), 17.8 ($SiC(CH_3)_3$), -4.3, -5.2 ($SiCH_3$); ν_{max} (film) 3546, 2957, 2930, 2887, 2857, 1735, 1498, 1472, 1462, 1251, 1099, 1045, 896, 835, 777, 695 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{13}H_{26}O_4Si+Na)^+$, 297.1492; found 297.1519.

9.6.5 (1*S*,6*R*)-methyl 1,6-bis((*tert*-butyldimethylsilyl)oxy) cyclohexa-2,4-dienecarboxylate

and

9.6.6 (1*S*,6*R*)-methyl 6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy cyclohexa-2,4-dienecarboxylate



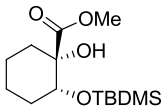
432 **431**

To a stirred solution of **121** (639 mg, 3.7 mmol) dissolved in CH_2Cl_2 (20 mL) was added triethylamine (0.71 mL, 5.8 mmol, 1.4 equiv) and *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.86 mL, 3.7 mmol, 1 equiv). The solution was stirred at room temperature for 4 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10-20% EtOAc-petrol) to yield a colourless oil **432** (40 mg, 3%), **431** (1.00 g, 95%).

432: R_f = 0.85 (20 % EtOAc-petrol); $[\alpha]_D^{25}$ +54 (*c* 1.62, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 6.03 (1H, ddd, *J* = 9.5, 4.5, 1.0 Hz), 5.74 – 5.89 (3H, m), 5.01 (1H, t, *J* = 1.0 Hz), 3.75 (3H, s), 0.88 (9H, s), 0.85 (9H, s), 0.08 (3H, s), 0.06 (3H, s), 0.01 (3H, s), 0.00 (3H, s); δ_c (75 MHz, $CDCl_3$) 175.1 (C=O), 135.2, 127.1, 125.8, 121.6 (C=C), 77.6 (COSi), 73.9 (CH(OSi)), 52.1 (OCH_3), 25.7, 25.6, 18.7, 17.9, -3.10, -3.15, -4.39, -5.05 ($SiCH_3$); ν_{max} (film) 2953, 2929, 2890, 2850, 1756, 1472, 1389, 1250, 1134, 1060, 1039, 809, 834, 775 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{20}H_{38}O_4Si_2+Na)^+$, 421.2201; found 421.2265.

431: R_f = 0.50 (20 % EtOAc-petrol); $[\alpha]_D^{25}$ -46 (*c* 1.3, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 6.14 (1H, dd, *J* = 9.5, 5.0 Hz), 5.93 (1H, dddd, *J* = 6.0, 5.0, 4.0, 2.5 Hz), 5.81 (1H, dd, *J* = 9.5, 1.0 Hz), 5.69 (1H, dquint, *J* = 9.5, 1.0 Hz), 4.97 (1H, quint, *J* = 2.0 Hz), 3.81 (3H, s), 3.41 (1H, s), 0.90 (9H, s), 0.12 (3H, s), 0.03 (3H, s); δ_c (75 MHz, $CDCl_3$) 175.3 (C=O), 131.9, 126.4, 124.8, 122.6 (C=C), 74.6 (COH), 72.7 (CH(OSi)), 52.9 (OCH_3), 25.6 ($SiC(CH_3)_3$), 17.9($SiC(CH_3)_3$), -4.4, -5.2 ($SiCH_3$); ν_{max} (film) 3516, 2959, 2929, 2863, 1736, 1494, 1453, 1252, 1111, 889, 777, 698 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{14}H_{24}O_4Si+Na)^+$, 307.1337; found 307.1389.

9.6.7 (1*S*,2*R*)-methyl 2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclohexanecarboxylate



433

A stirred solution of **431** (1.00 g, 3.5 mmol) and Pd/C (50 mg, 10 wt.% loading, matrix activated carbon support) in MeOH (50 mL) was exposed to a hydrogen atmosphere at room temperature. After 24 h the solution was filtered through a plug of celite and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10-50% EtOAc-petrol) to yield a colourless oil **433** (375 mg, 42%), **387** (360 mg, 58%).

433: R_f = 0.60 (20% EtOAc-petrol); $[\alpha]_D^{25}$ -7.0 (*c* 1.3, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 3.94 (1H, dd, *J* = 10.5, 5.0 Hz), 3.72 (3H, s), 3.05 (1H, d, *J* = 1.5 Hz), 1.91 – 1.14 (8H, m), 0.83 (9H, s) 0.04 (3H, s), -0.03 (3H, s); δ_c (75 MHz, $CDCl_3$) 176.1 (C=O), 77.5 (C(OH)), 73.8 (CH(OSi)), 33.1, 30.1 (CH), 25.6 (SiC(*C*H_3)$_3$), 23.8, 19.6 (CH), 17.8 (Si*C*(CH_3)$_3$), -4.1, -5.2 ($SiCH_3$); ν_{max} (film) 3555, 3027, 2928, 1705, 1494, 1453, 1281, 908, 732, 699 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{14}H_{28}O_4Si+H)^+$, 289.1835; found 289.1831.

9.6.8 (1*R*,2*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohexane-1,2-diol

and

9.6.9 (1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-(hydroxymethyl) cyclohexanol

434 **430**

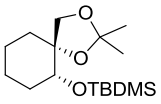
To a stirred solution of **433** (375 mg, 1.3 mmol) in THF at -78 °C was added dropwise $LiAlH_4$ (0.54 mL, 2.4 M solution, 1.3 mmol, 1 equiv) over 20 mins. The resulting solution was left to warm to room temperature for 12 h. Solution was quenched with addition of H_2O (0.05 mL) followed by NaOH (10% aq. sol. 0.09 mL) followed by H_2O (0.14 mL). The solution was filtered through $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5-20% EtOAc-petrol) to yield a colourless oil **434** (19 mg, 5%), **430** (45 mg, 13%).

To a stirred solution of **433** (465 mg, 1.6 mmol) in THF at -78 °C was added dropwise $LiBH_4$ (0.8 mL, 4.0 M solution, 3.22 mmol, 2 equiv) over 20 mins. The resulting solution was left to warm to room temperature for 12 h. Solution was quenched with addition of Et_2O (10 mL) followed by H_2O (10 mL). The mixture was separated, and the aqueous layer extracted with EtOAc (4 × 10 mL), the organic layers were combined and dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5-20% EtOAc-petrol) to yield a **430** (400 mg, 91%).

434: R_f = 0.55 (20 % EtOAc-petrol); $[\alpha]_D^{25}$ +10 (*c* 0.5, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 3.66 (1H, d, *J* = 10.0, Hz), 3.64 (1H, dd, *J* = 10.0, 4.5 Hz), 3.52 (1H, d, *J* = 10.0 Hz), 1.73-1.63 (3H, m), 1.60-1.50 (2H, m), 1.45-1.39 (1H, m), 1.22-1.08 (2H, m), 0.90 (9H, s), 0.09 (3H, s), 0.08 (3H, s); δ_c (125 MHz, $CDCl_3$) 73.7, 71.9, 71.8, 31.8, 29.5, 25.8 ($SiC(CH_3)_3$), 23.5, 20.3, 18.1 ($SiC(CH_3)_3$), -5.5, -5.6 ($SiCH_3$); ν_{max} (film) 3555, 3027, 2929, 1494, 1453, 1218, 908, 732, 699 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{13}H_{28}O_3Si+H)^+$, 261.1886; found 261.1858.

430: R_f = 0.45 (20 % EtOAc-petrol); $[\alpha]_D^{25}$ -18 (*c* 0.5, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 3.65 (1H, br s), 3.56 (1H, d, *J* = 10.0 Hz), 3.37 (1H, d, *J* = 10.0 Hz), 2.51 (2H, br s, OH), 1.82 (1H, d, *J* = 13.0 Hz), 1.63 (3H, m), 1.52 (1H, m), 1.40 (1H, m), 1.29 (1H, m), 1.19-1.14 (1H, m); δ_c (125 MHz, $CDCl_3$) 73.2, 72.9 (CH), 68.3 (OCH_2), 31.7, 30.7, 25.8 ($SiC(CH_3)_3$), 23.1, 20.7, 17.9 ($SiC(CH_3)_3$), -4.0, -4.9 ($SiCH_3$); ν_{max} (film) 3443, 2930, 2857, 1463, 1389, 1261, 1252, 1079, 835, 777 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{13}H_{28}O_3Si+H)^+$, 261.1886; found 261.1886.

9.6.10*tert*-butyl(((5*R*,6*R*)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-yl)oxy)dimethylsilane

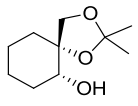


435

To a stirred solution of **430** (1.81 g, 6.59 mmol) dissolved in acetone (10 mL, freshly distilled), was added 2,2-Dimethoxypropane (12 mL, 100 mmol) and *para*-toluenesulfonic acid (13 mg, 0.06 mmol, 10 mol %). The solution was stirred at room temperature for 20 h. The resulting solution was diluted with EtOAc (10 mL) followed by the addition of water (20 mL). The biphasic system was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10-20% EtOAc-petrol) to yield **435** a colourless oil (1.72 g, 86%).

R_f = 0.80 (10% EtOAc-petrol); $[\alpha]_D^{25}$ -20 (*c* 0.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 3.88 (1H, d, *J* = 8.0 Hz), 3.70 (1H, d *J* = 8.0 Hz), 3.53 (1H, dd, *J* = 7.0, 3.0 Hz), 1.95-1.86 (1H, m), 1.75-1.56 (3H, m), 1.51-1.18 (4H, m) 1.39 (6H, s, CH_3), 0.90 (9H, s), 0.07 (3H, s), 0.05 (3H, s); δ_c (75 MHz, $CDCl_3$) 109.2, 83.4, 72.8, 70.8, 34.0, 32.3, 27.8, 26.9, 25.9, 22.6, 21.6, 18.2, -4.5, -4.6; ν_{max} (film) 2988, 2933, 2894, 2856, 1472, 1462, 1377, 1368, 1251, 1212, 1141, 1094, 1056, 988, 898, 773 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{16}H_{32}O_3Si+Na)^+$, 323.2018; found 323.2015.

9.6.11(5*R*,6*R*)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-ol

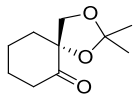


436

To a stirred solution of **435** (1.72 g, 5.72 mmol) in THF (50 mL) at -78 °C, was added dropwise Tetrabutylammonium fluoride hydrate (1M solution in THF, 5.72 mL, 2 equiv) over 5 mins. The resulting solution was allowed to warm to room temperature over 16 h. The resulting solution was quenched with Et_2O (10 mL) and $NH_3Cl_{(aq)}$ (10 mL). The organic layer was extracted with EtOAc (4 × 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5% EtOAc-petrol) to yield **436** a colourless oil (591 mg, 55%).

R_f = 0.30 (20% EtOAc-petrol); $[\alpha]_D^{25}$ -4.0 (*c* 0.9, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 3.99 (1H, d, *J* = 8.5 Hz), 3.71 (1H, d, *J* = 8.5 Hz), 3.49 (1H, m), 2.11 (1H, br s, OH), 1.99 – 1.23 (8H, m), 1.40 (3H, s), 1.39 (3H, s); δ_c (100 MHz, $CDCl_3$) 109.4, 83.2, 71.5, 71.3, 33.7, 33.2, 29.7, 27.2, 27.1, 22.6; ν_{max} (film) 3204, 2930, 2855, 1563, 1406, 1371, 1184, 903, 729 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{10}H_{18}O_3+Na)^+$, 209.1149; found 209.1104.

9.6.12(*R*)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-one



429

Oxalyl chloride (0.10 mL, 1.18 mmol, 2 equiv) followed by Dimethyl sulfoxide (0.08 mL, 1.18 mmol, 2 equiv) was added to a flask containing CH_2Cl_2 (2 mL) and stirred at -78 °C for 15 mins. Alcohol **436** (110 mg, 0.59 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise to the cooled solution and left to stir at -78 °C for 1 h. Triethylamine (0.5 mL, 3.54 mmol, 6 equiv) was added dropwise at -78 °C and left to stir for 20 mins, before allowing to slowly warm to room temperature. The reaction was quenched with the addition of water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (4 x 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (5% EtOAc-petrol) to yield **429** a colourless oil (32 mg, 30%).

Or

To alcohol **436** (591 mg, 3.17 mmol) dissolved in CH_2Cl_2 (50 mL) was added Dess–Martin periodinane (2.69 g, 6.3 mmol, 2 equiv) the solution and left to stir at room temperature for 72 h. The reaction was quenched with the addition of water (20 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL) and the organic layers combined and washed with saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (10% EtOAc-petrol) to yield **429** a colourless oil (517 mg, 86%).

R_f = 0.50 (20% EtOAc-petrol); $[\alpha]_D^{25}$ -6.0 (*c* 1.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.42 (1H, d, *J* = 8.5), 3.65 (1H, d, *J* = 8.5 Hz), 2.78 (1H, ddd, *J* = 15.0, 9.0, 5.0 Hz), 2.34 – 2.27 (1H, m), 2.04 – 1.86 (3H, m), 1.80 – 1.59 (3H, m), 1.40 (3H, s), 1.33 (3H, s); δ_c (100 MHz, $CDCl_3$) 209.1, 110.5, 85.6, 69.1, 39.7, 28.5, 27.4, 26.9, 26.1, 22.3; ν_{max} (film) 2986, 2937, 2865, 1723, 1452, 1431, 1380, 1371, 1050, 858, 811 cm^{-1}; HRMS (ESI+) m/z calcd for $(C_{10}H_{16}O_3+Na)^+$, 207.0997; found 207.0995.

9.7 Chapter 6 Experimental.

9.7.1 General Method for epoxidation of styrene.

Any variations from this general procedure, reaction optimisation etc, are detailed in Chapter 6.

Styrene (0.1 mL, 0.87 mmol, 1 equiv) in CH_3CN (0.8 mL) was added *N,N*-Dimethylpyridin-4-amine (18 mg, 0.16 mmol, 20 mol%), H_2O_2 (1.0 mL, 35 wt%, 12 equiv), N,N'-Diisopropylcarbodiimide (219 mg, 1.74 mmol, 2 equiv) and acid catalyst (0.1 equiv). The resulting solution was stirred at r.t, for 20 h. At this point the reaction was quench with the addition of $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressue. The crude mixture was analysed via NMR spectroscopy to obtain conversion to styrene oxide, and chiral HPLC to calculate any enantioselectivity.

Chiral HPLC methods were developed for styrene oxide: Method 1: Chiralpak AS. 0.2 $mlmin^{-1}$. 0.6% IPA/Hexane, 254nm. t_1 = 30 mins and t_2 = 35 mins. Method 2: Chiralpak AS. 0.8 $mlmin^{-1}$. 0.2% IPA/Hexane, 254nm. t_1 = 9.9 mins and t_2 = 12.4 mins.

9.7.2 Sulfide oxidation to test for prescence of peracid

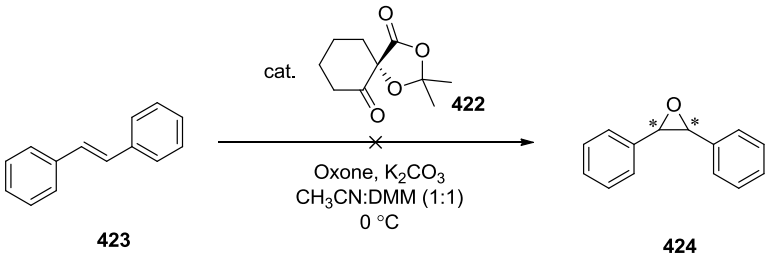
Experiment 1: Benzoic acid (94 mg, 0.78 mmol, 1 equiv), DIC (0.24 mL, 1.54 mmol, 2 equiv), DMAP (19 mg, 0.16 mmol, 10 mol%) H_2O_2 (35 wt%, 0.79 mL, 12 equiv), thioanisole (484 mg, 3.9mmol, 5 equiv) MeCN (0.8 mL). Stirred r.t., 15 mins. Workup, add ice (5 mL), add $NaHCO_{3(aq)}$ extract $CHCl_3$ (3 × 10 mL), dry $MgSO_4$ concentrate under reduced pressure.

Experiment 2: Chiral acid **384** (68 mg, 0.34 mmol, 1 equiv), DIC (0.1 mL, 0.68 mmol, 2 equiv), DMAP (8 mg, 0.06 mmol, 10 mol%) H_2O_2 (35 wt%, 0.35 mL, 12 equiv), thioanisole (217 mg, 1.75mmol, 5 equiv) MeCN (0.35 mL). Stirred r.t., 60mins. Standard workup.

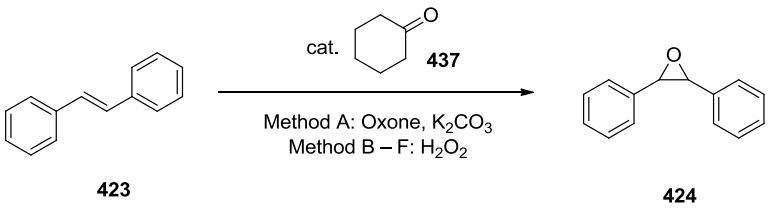
Experiment 3: DIC (0.1 mL, 0.68 mmol, 2 equiv), DMAP (8 mg, 0.06 mmol, 10 mol%) H_2O_2 (35 wt%, 0.35 mL, 12 equiv), thioanisole (217 mg, 1.75mmol, 5 equiv) MeCN (0.35 mL). Stirred r.t., 60mins. Standard workup.

Experiment 4: Benzoic acid (94 mg, 0.78 mmol, 1 equiv), DIC (0.24 mL, 1.54 mmol, 2 equiv), DMAP (19 mg, 0.16 mmol, 10 mol%) H_2O_2 (35 wt%, 0.79 mL, 12 equiv), thioanisole (484mg, 3.9mmol, 5 equiv) MeCN (0.8 mL). Stirred r.t., 15mins. Standard workup.

9.8 Epoxidation conditions Chapter 7.



Epoxidation of *trans*-stilbene with chiral ketone 422. *trans*-stilbene (90 mg, 0.5 mmol), ketone **422** (14 mg, 10 mol%), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.03 mmol) in MeCN-DMM (v/v, 1/2) (9 mL) was added buffer (0.05 M aq Na_2HPO_4-0.05 M aq KH_2PO_4, pH 7.0) (3 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.212 M in 4×10^{-4} M aq EDTA, 4.8 mL) and a solution of K_2CO_3 (0.42 M in 4×10^{-4} M aq EDTA, 4.8 mL) were added dropwise over 1 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.



Method A: *trans*-stilbene (180 mg, 1.0 mmol), cyclohexanone (0.03 mL, 30 mol%), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.04 mmol) in MeCN-DMM (v/v, 1:2) (15 mL) was added buffer (10 mL, 0.05 M aq $Na_2B_4O_7 \cdot 10H_2O$ in 4×10^{-4} M aq Na_2(EDTA)). The mixture was cooled to 0 °C in an ice bath. A solution of Oxone (1.0 g, 1.6 mmol in 6.5 mL 4×10^{-4} M aq Na_2(EDTA)), and a solution of K_2CO_3 (0.93 g, 6.74

mmol H_2O 6.5 mL), were added dropwise separately and simultaneously via syringe pump over 2 h. The reaction was quenched by addition of pentane and extracted with pentane (4 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

Method B: To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and cyclohexanone (0.03 mL, 30 mol%) in MeCN-DMM (v/v, 1:2) (6 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq $Na_2(EDTA)$). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C. The reaction was left to room temperature over 48 h. Reaction was quenched and extracted as per Method A.

Method C: To a solution of *trans*-stilbene (180 mg, 1.0 mmol), cyclohexanone (0.03 mL, 30 mol%), MeCN (0.2 mL, 3.8 mmol), *n*-BuOH (3.0 mL) was added buffer solution (3.5 mL, 0.3 M K_2CO_3 in 4×10^{-4} M aq $Na_2(EDTA)$). Followed by H_2O_2 (35%, 0.25 mL, 3 mmol) at 0 °C and left to warm to room temperature over 24 h. Reaction was quenched and extracted as per Method A.

Method D: To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and cyclohexanone (0.03 mL, 30 mol%) in MeCN-EtOH-CH_2Cl_2 (v/v, 1:1:2) (2.0 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq $Na_2(EDTA)$). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C for 24h. Reaction was quenched and extracted as per Method A.

Method E: To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and catalyst (15 mol%) in MeCN-EtOH-CH_2Cl_2 (v/v, 1:1:2) (2.0 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq $Na_2(EDTA)$). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C for 24h. Reaction was quenched and extracted as Method A.

Method F: To a solution of *trans*-stilbene (180 mg, 1.0 mmol) and catalyst (1 equiv) in MeCN-EtOH-CH_2Cl_2 (v/v, 1:1:2) (2.0 mL) was added buffer solution (1.5 mL, 2.0 M K_2CO_3 in 4×10^{-4} M aq $Na_2(EDTA)$). Followed by H_2O_2 (30%, 0.25 mL, 3 mmol) at 0 °C for 72 h. Reaction was quenched and extracted as Method A.

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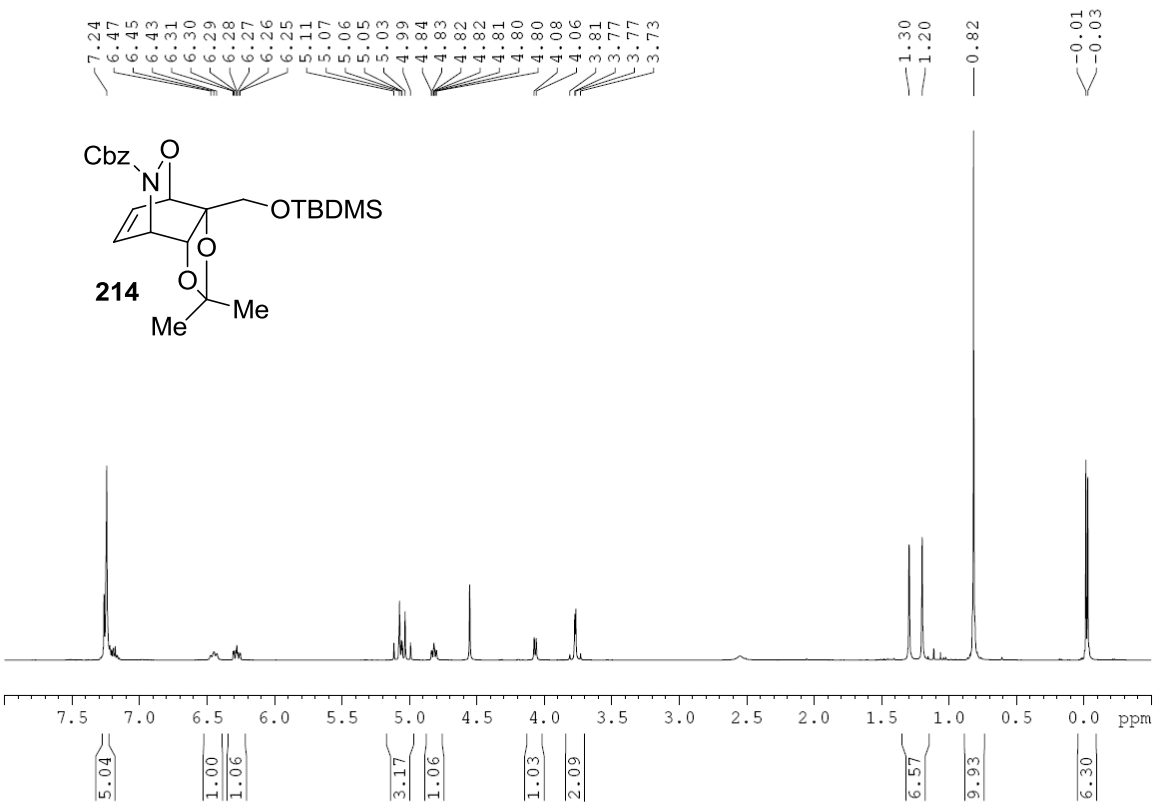
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5.03
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4.82
4.81
4.80
4.80
4.08
4.06
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3.77
3.73
1.30
1.20
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-0.03
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OTBDMS
O
O
Me
Me
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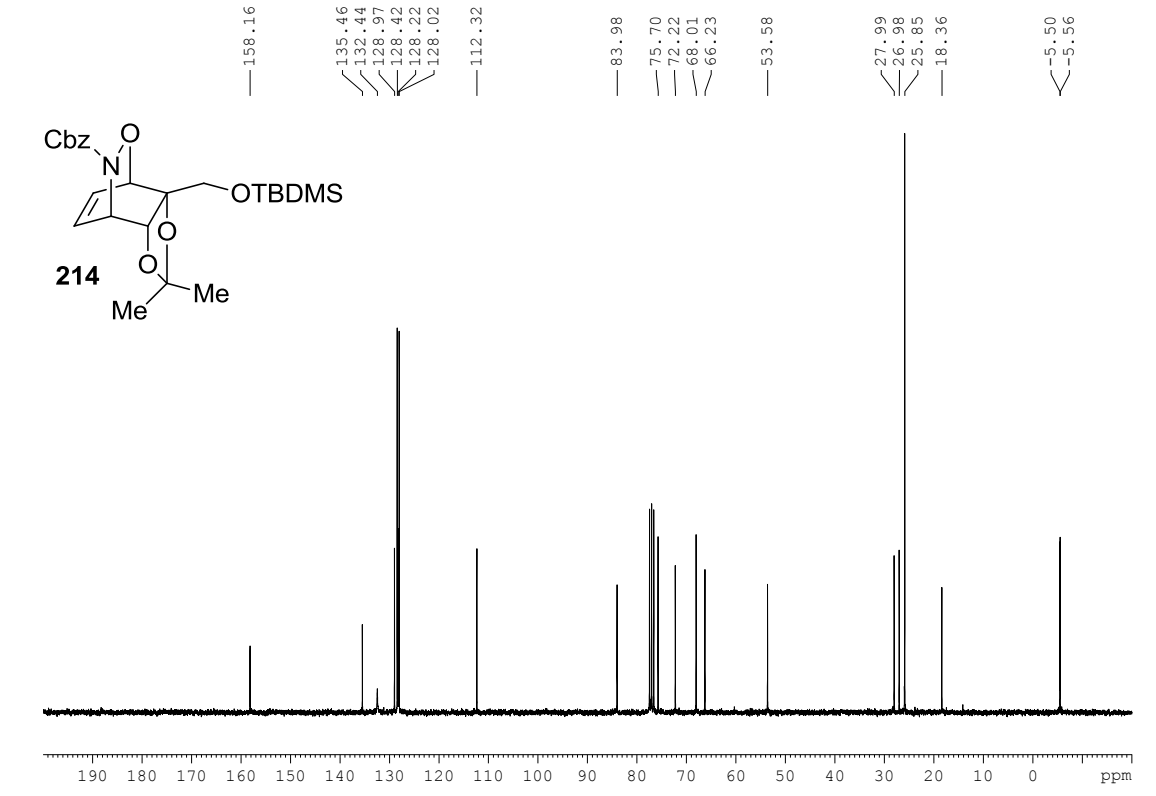
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25.85
18.36
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O
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Me
Me
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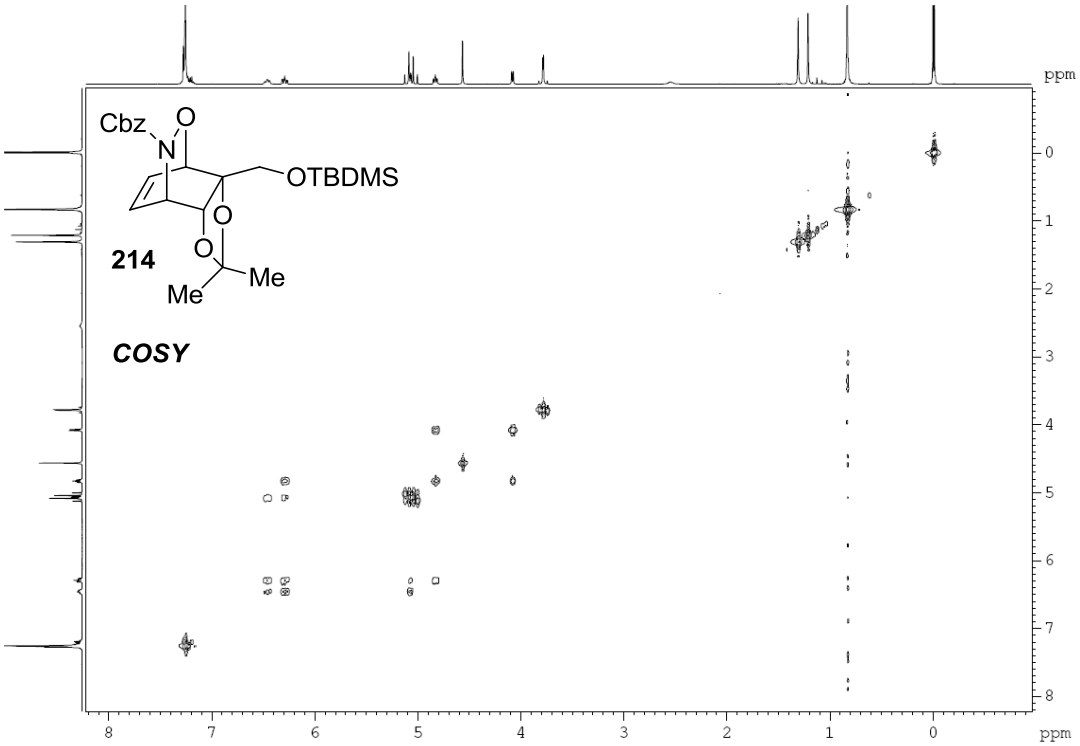
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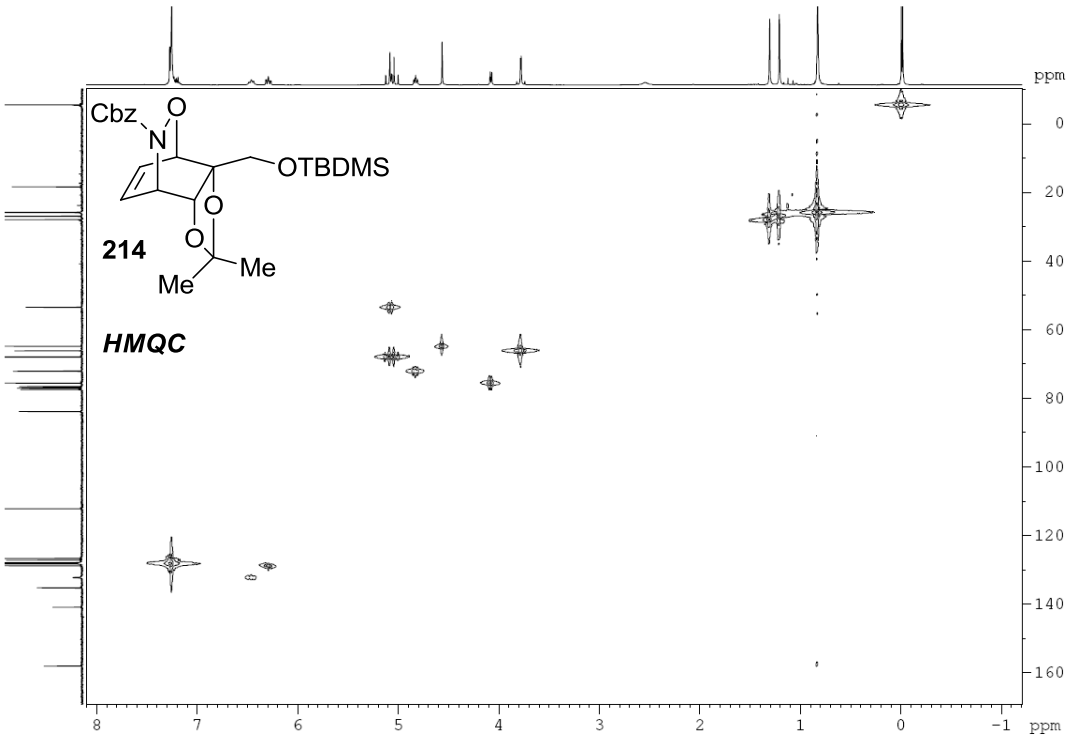
ppm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HMQC
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4
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1
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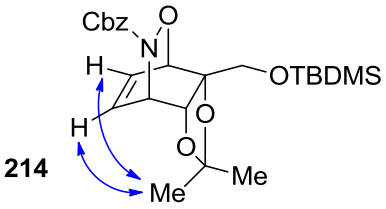
ppm



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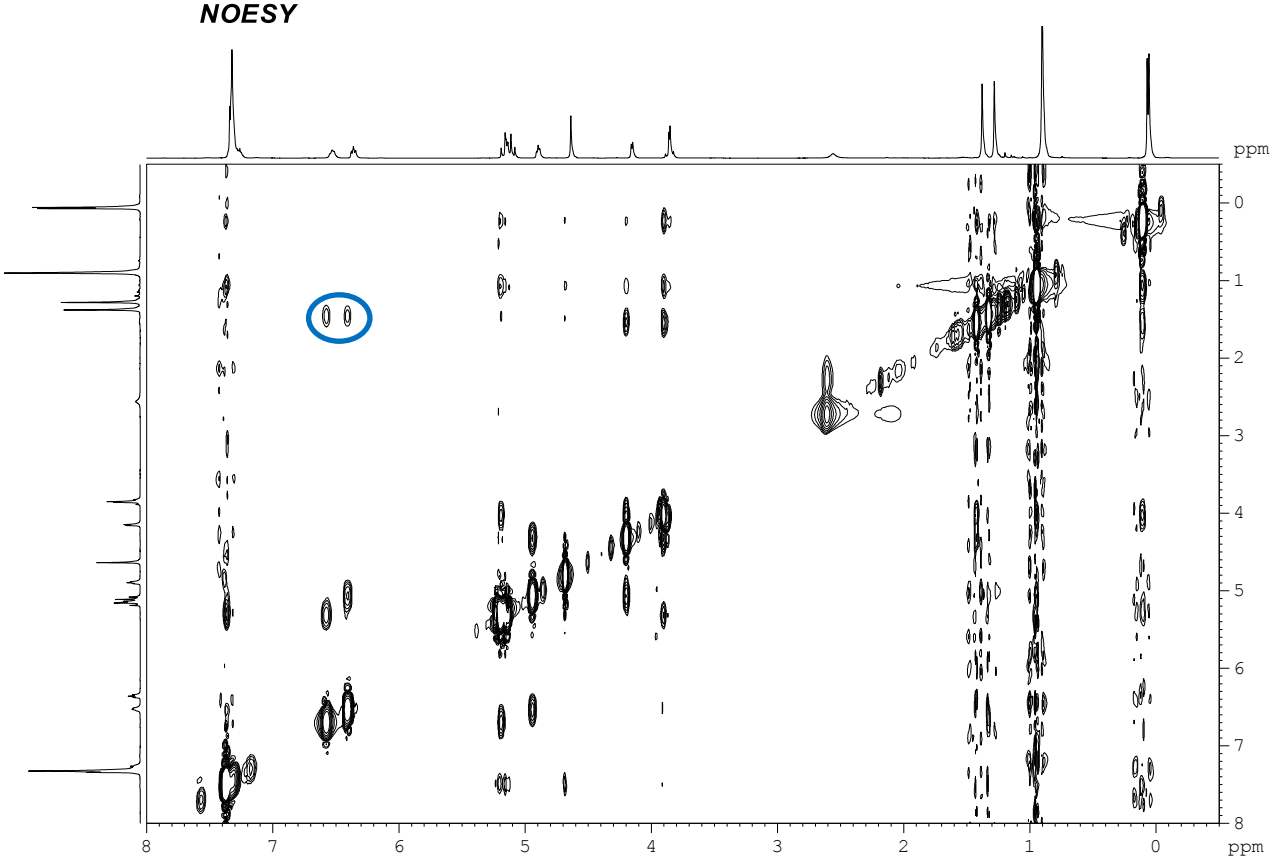

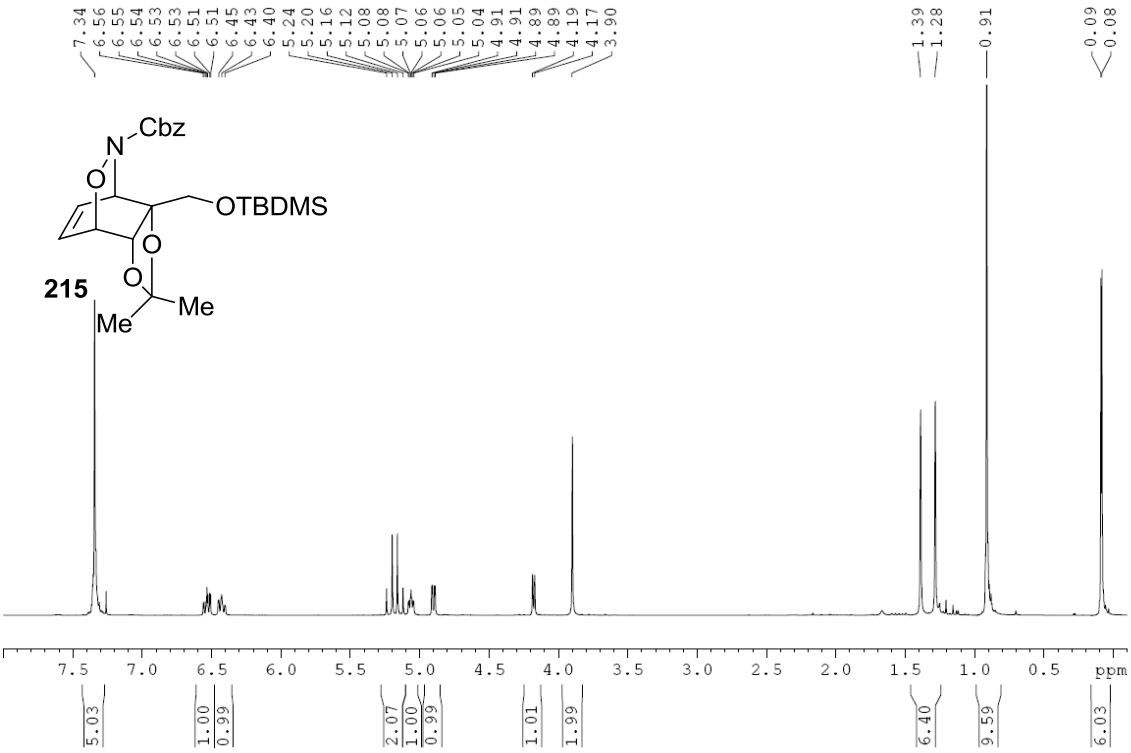
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5.16
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5.08
5.08
5.07
5.06
5.06
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5.04
4.91
4.91
4.89
4.89
4.19
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0.08
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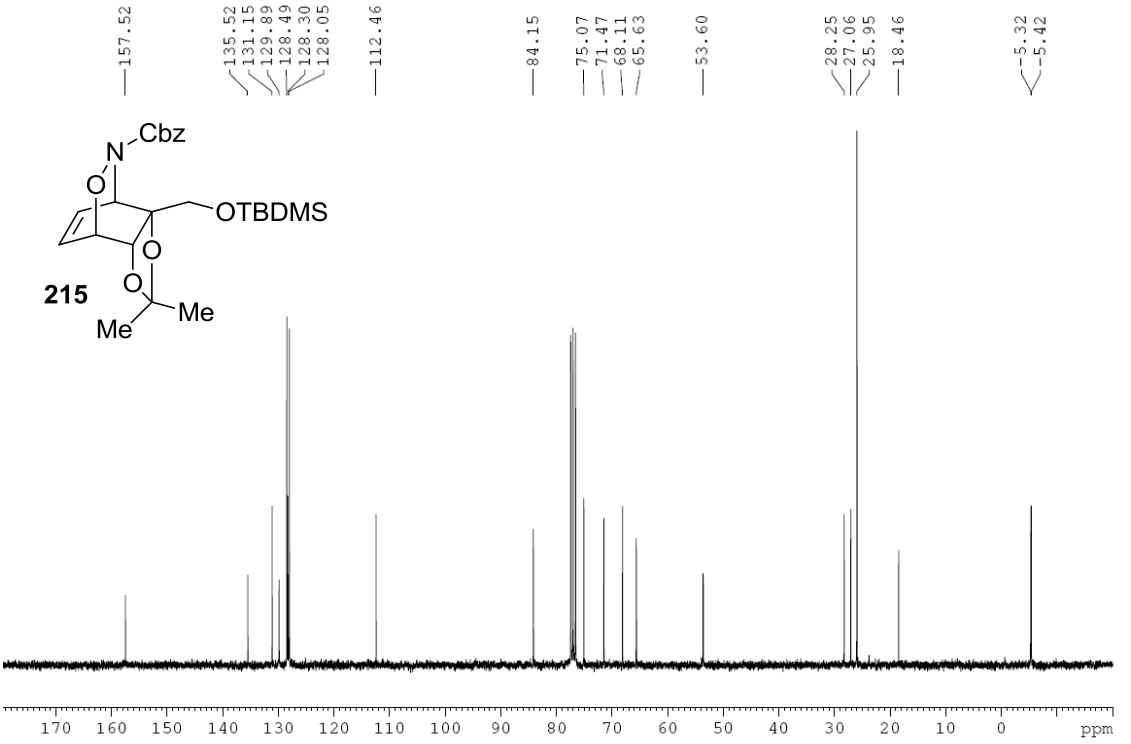
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OTBDMS
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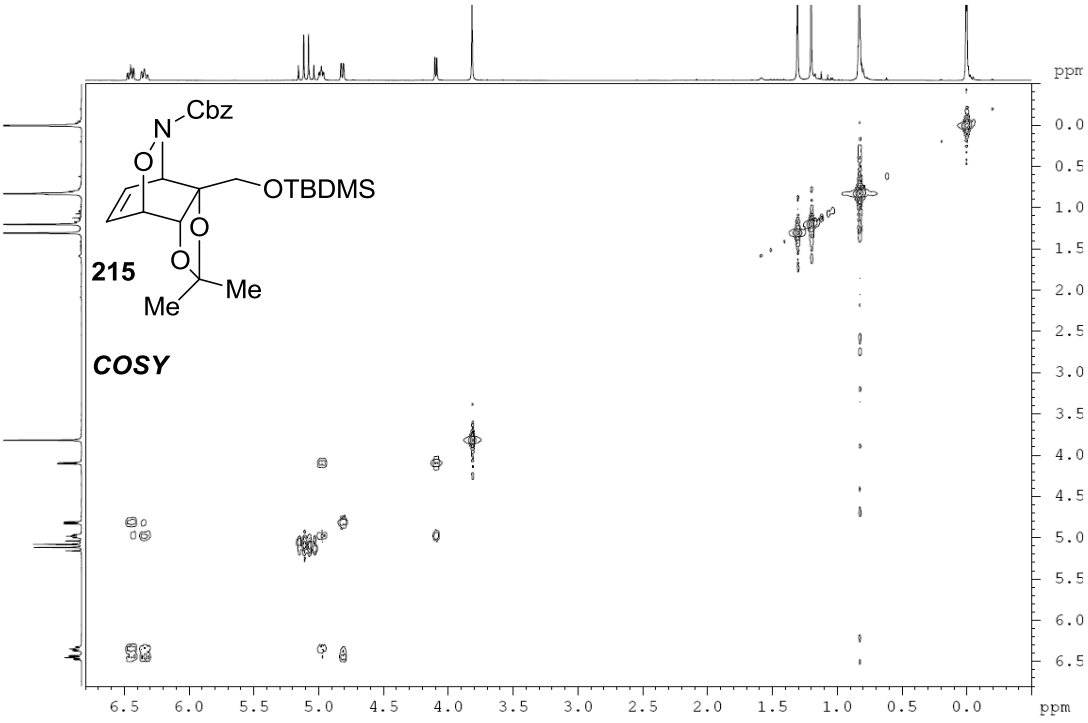
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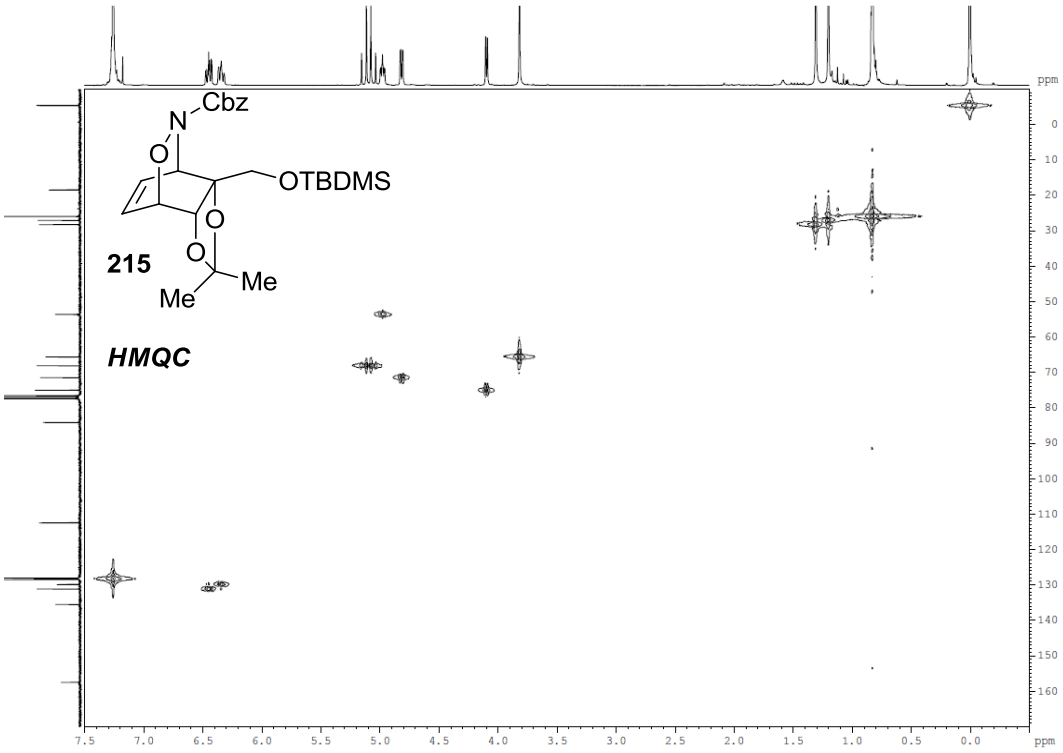
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100
110
120
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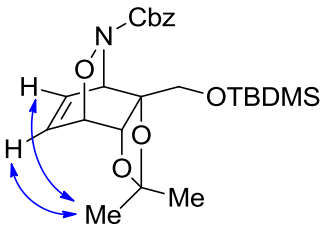

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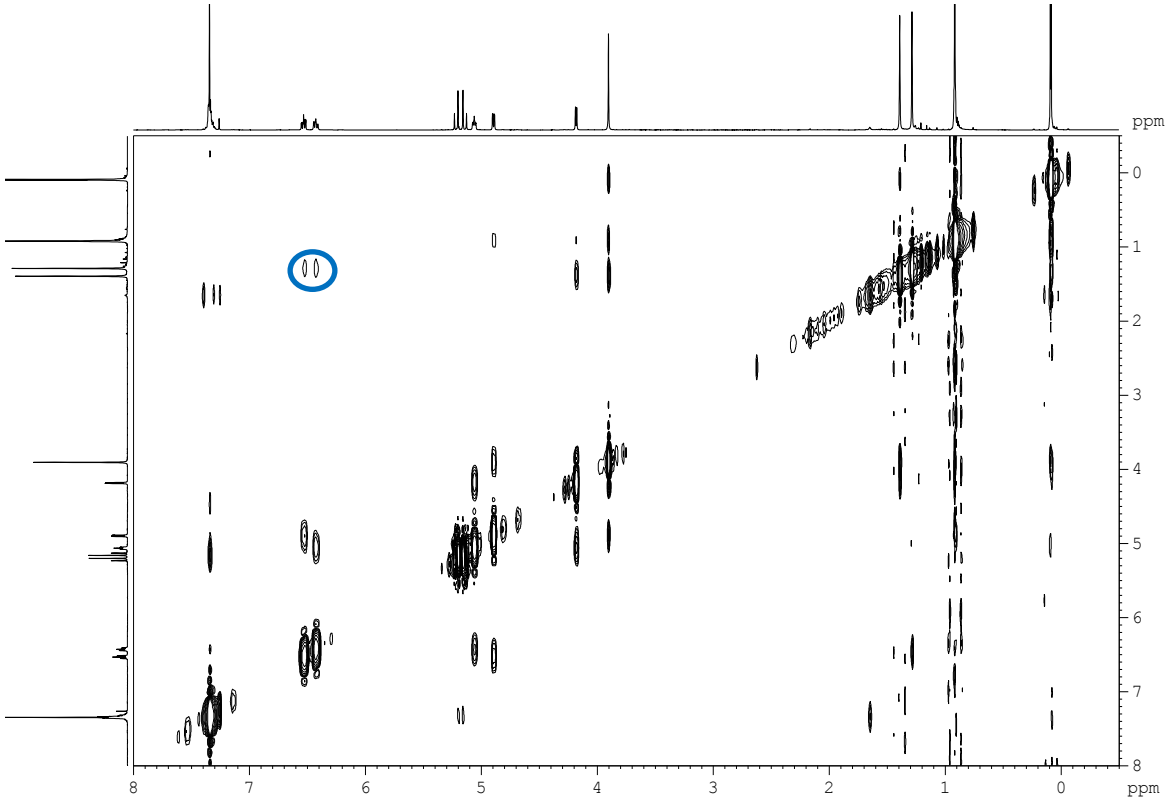

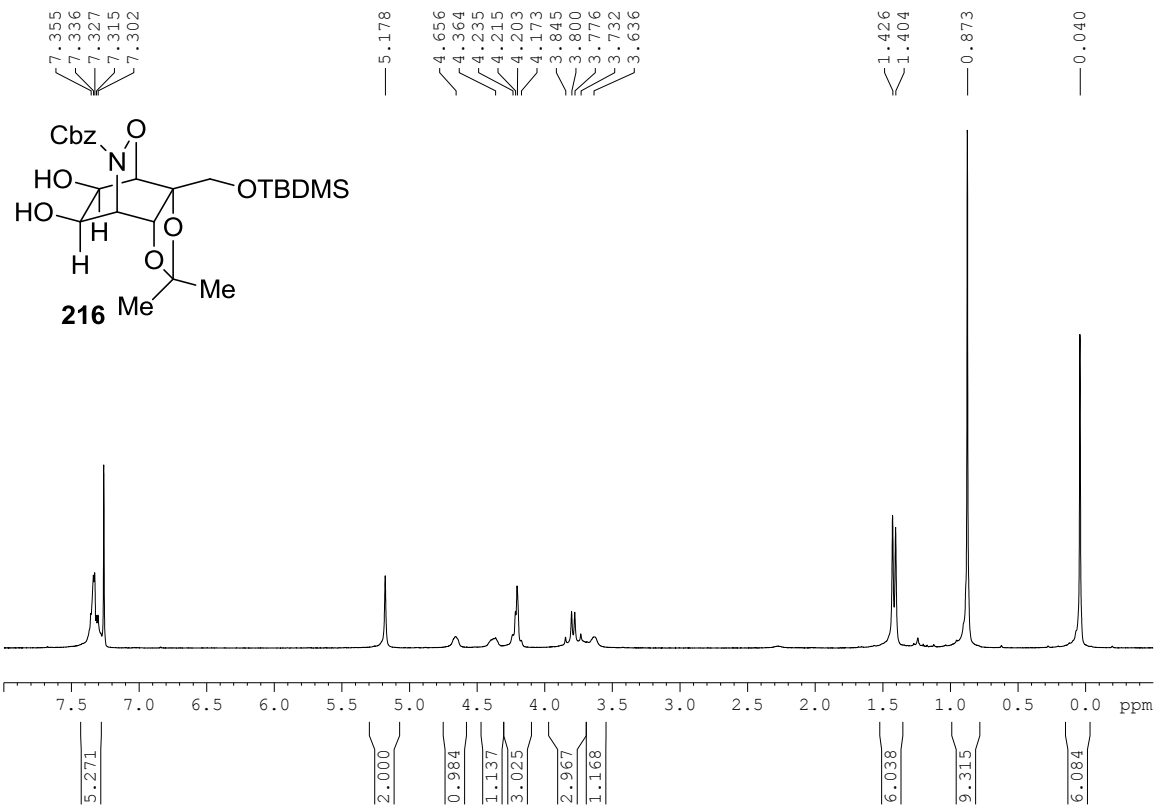
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3.800
3.776
3.732
3.636
1.426
1.404
0.873
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Cbz
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O
HO
HO
H
H
O
O
Me
Me
OTBDMS
216
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6.5
6.0
5.5
5.0
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4.0
3.5
3.0
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2.0
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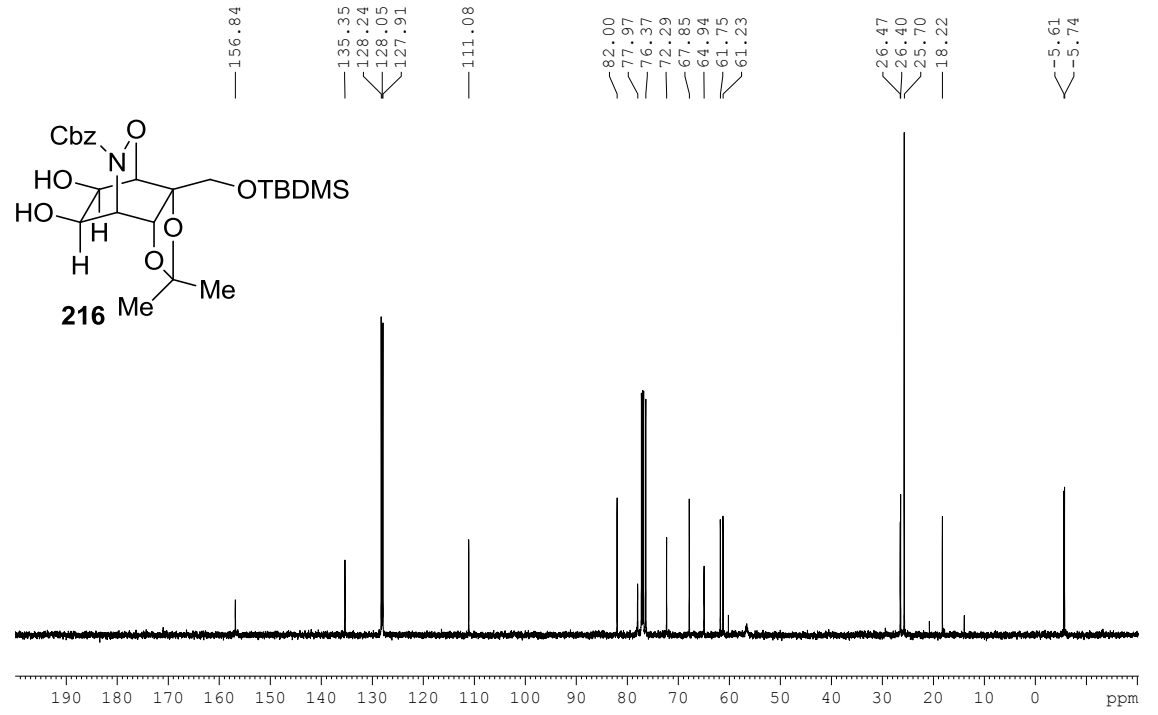
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72.29
67.85
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61.75
61.23
26.47
26.40
25.70
18.22
-5.61
-5.74
Cbz
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HO
HO
H
H
O
O
Me
Me
OTBDMS
216
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150
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130
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110
100
90
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70
60
50
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30
20
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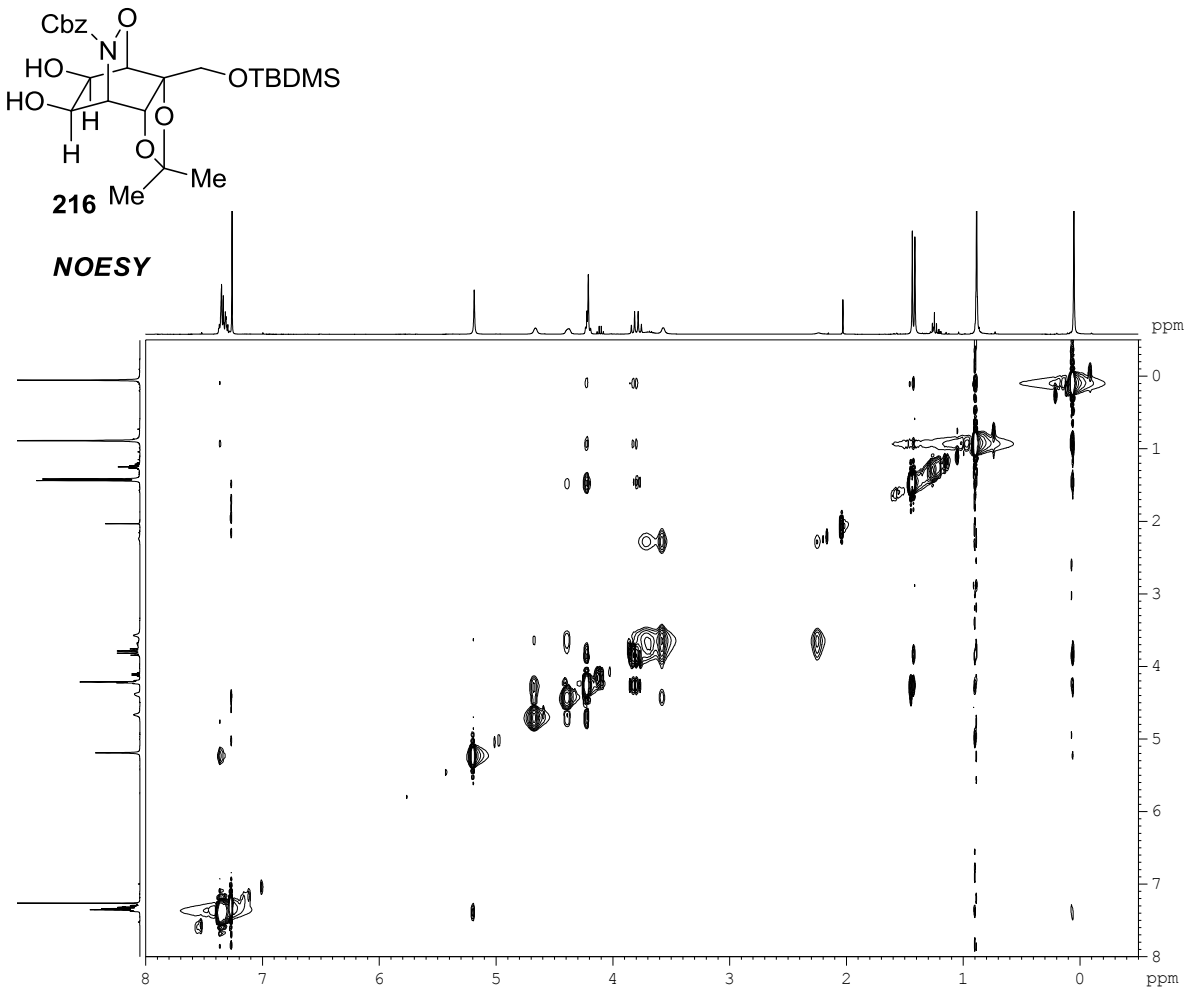
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NOESY
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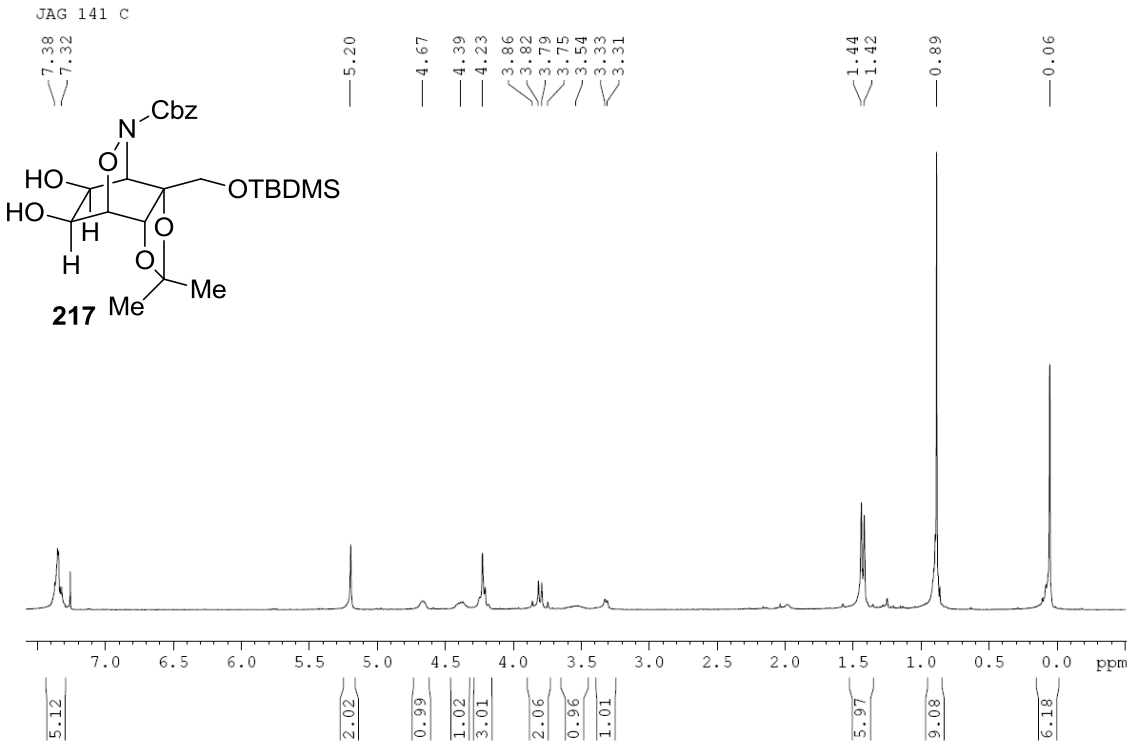
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3.33
3.31
1.44
1.42
0.89
0.06
Cbz
N
O
HO
HO
H
H
O
O
Me
Me
OTBDMS
217
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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1.02
3.01
2.06
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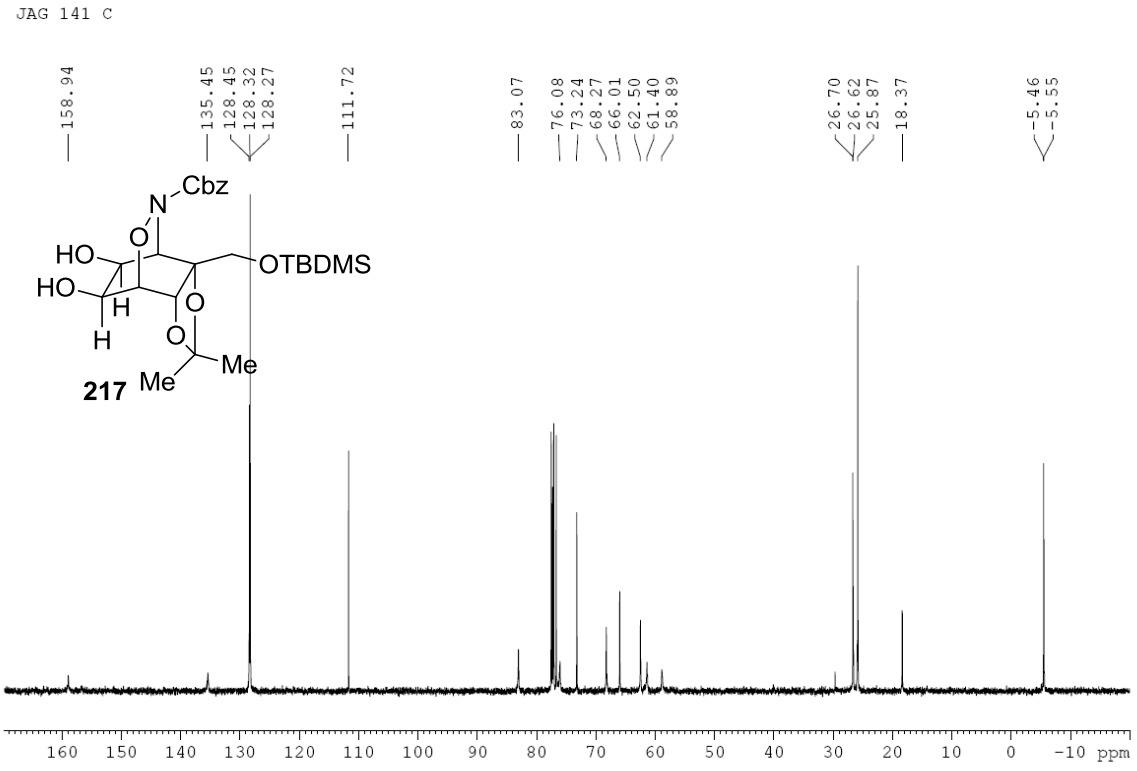
5.97
9.08
6.18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83.07
76.08
73.24
68.27
66.01
62.50
61.40
58.89
26.70
26.62
25.87
18.37
-5.46
-5.55
Cbz
N
O
HO
HO
H
H
O
O
Me
Me
OTBDMS
217
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130
120
110
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90
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50
40
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10
0
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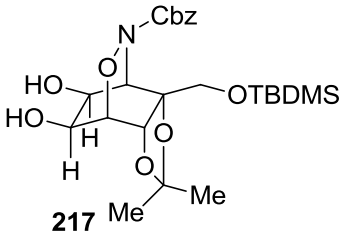
ppm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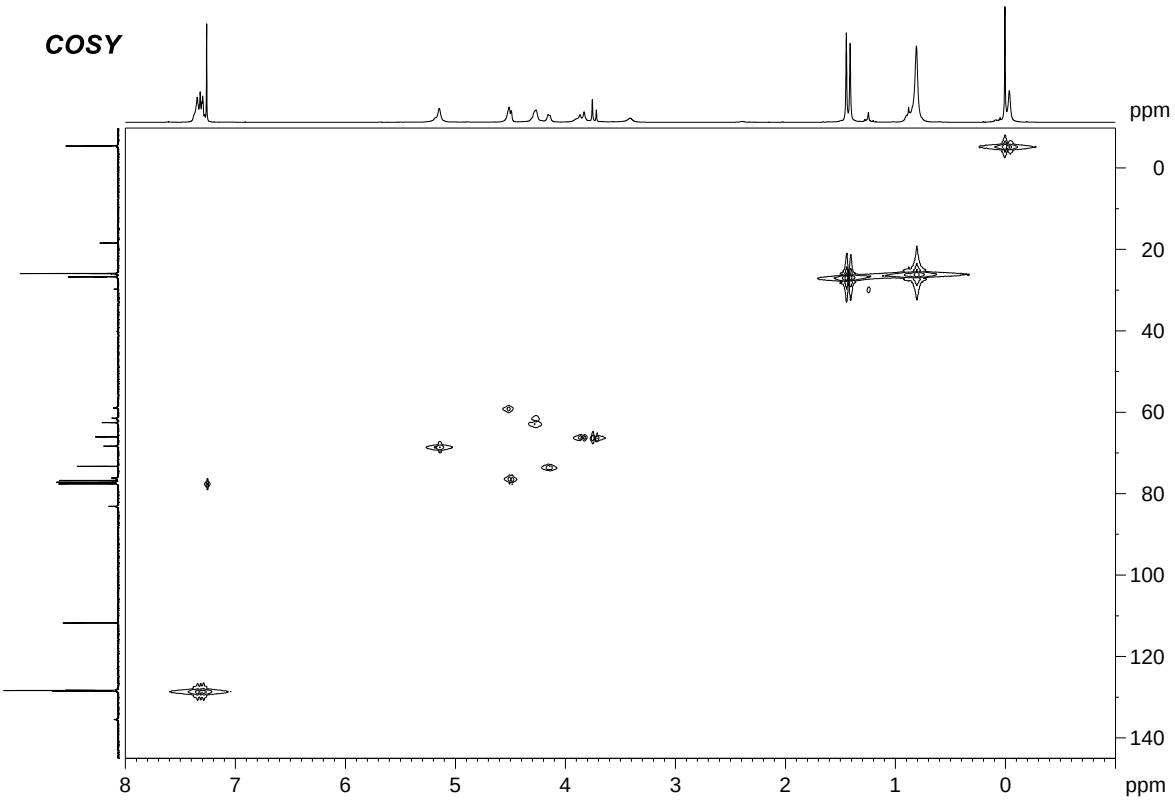
OTBDMS

217

COSY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1
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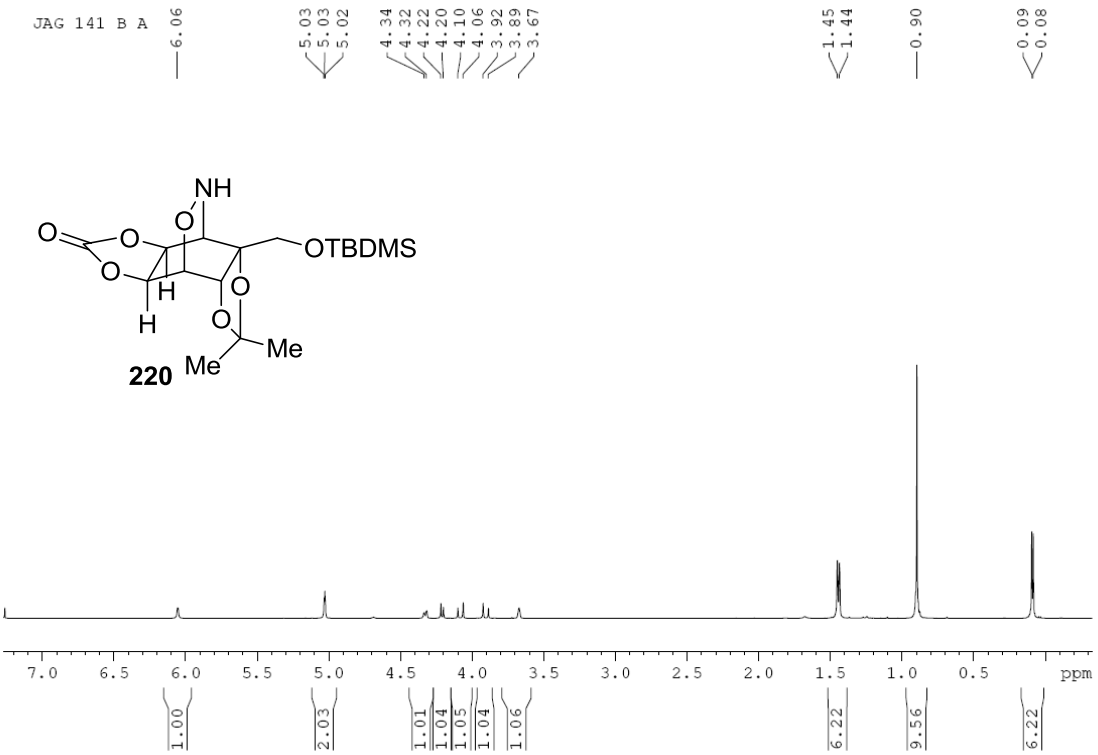
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4.20
4.10
4.06
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3.89
3.67
1.45
1.44
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0.09
0.08
NH
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O
O
O
H
H
O
O
Me
Me
OTBDMS
220
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6.5
6.0
5.5
5.0
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4.0
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3.0
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1.04
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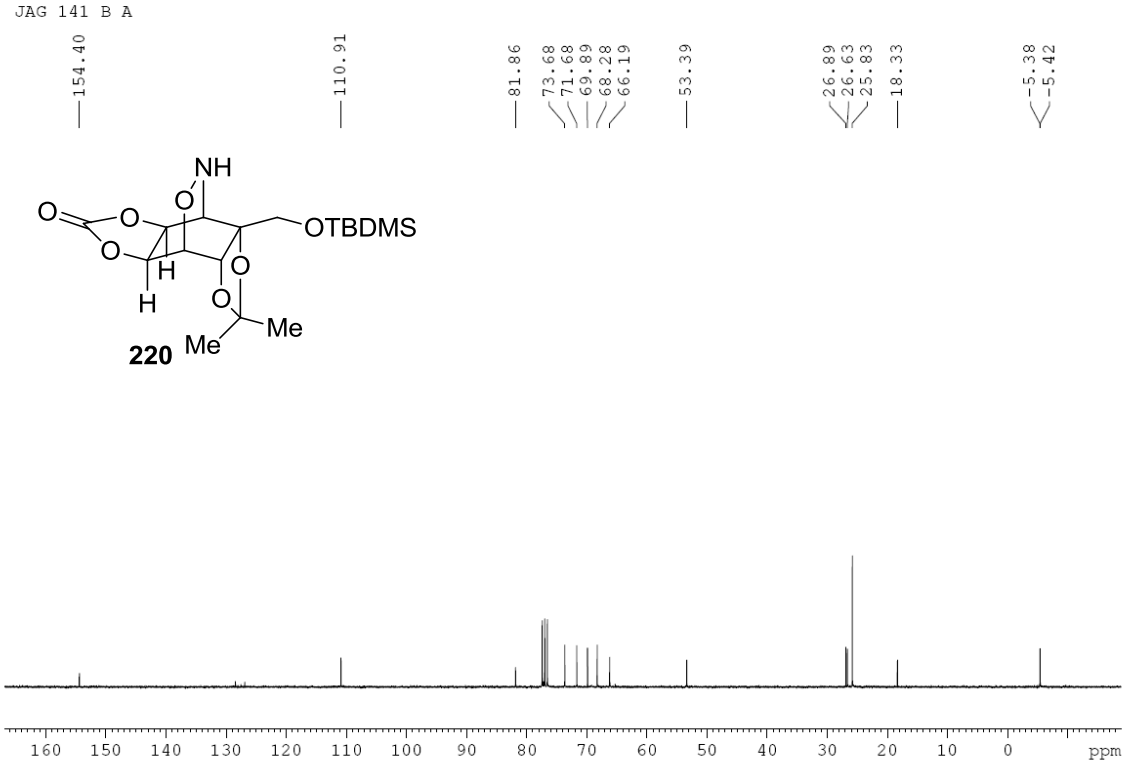
9.56
6.22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110.91
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73.68
71.68
69.89
68.28
66.19
53.39
26.89
26.63
25.83
18.33
-5.38
-5.42
NH
O
O
O
O
H
H
O
O
Me
Me
OTBDMS
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30
20
10
0
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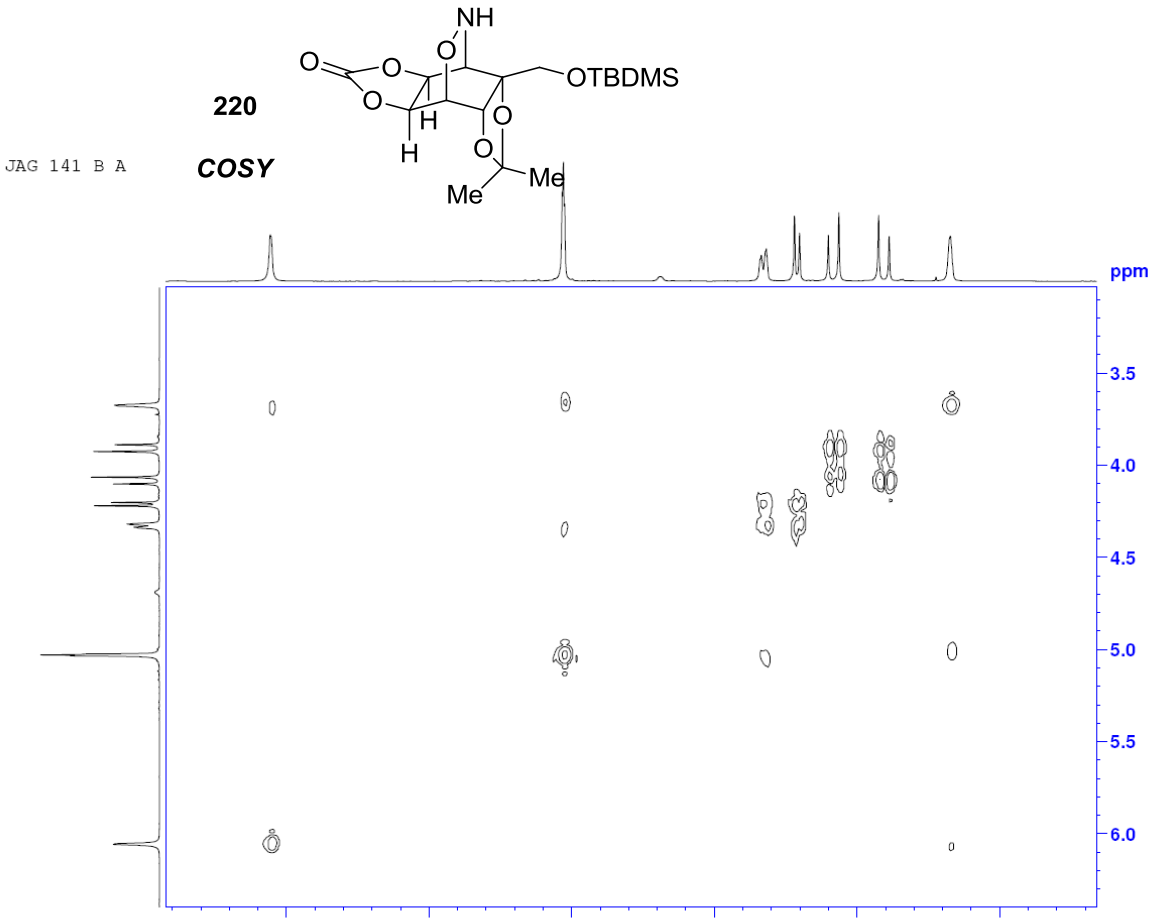
220
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COSY
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OTBDMS
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O
Me
Me
ppm
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4.0
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5.0
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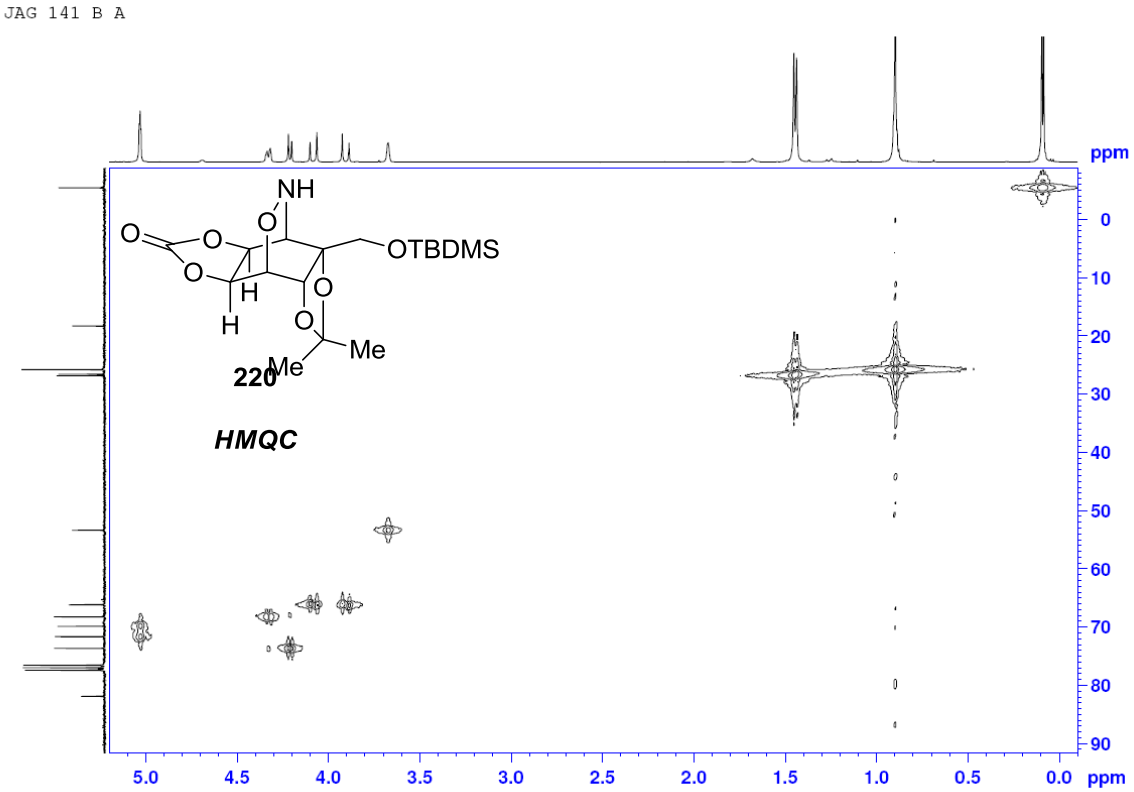
6.0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OTBDMS
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H
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O
Me
Me
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HMQC
ppm
0
10
20
30
40
50
60
70
80
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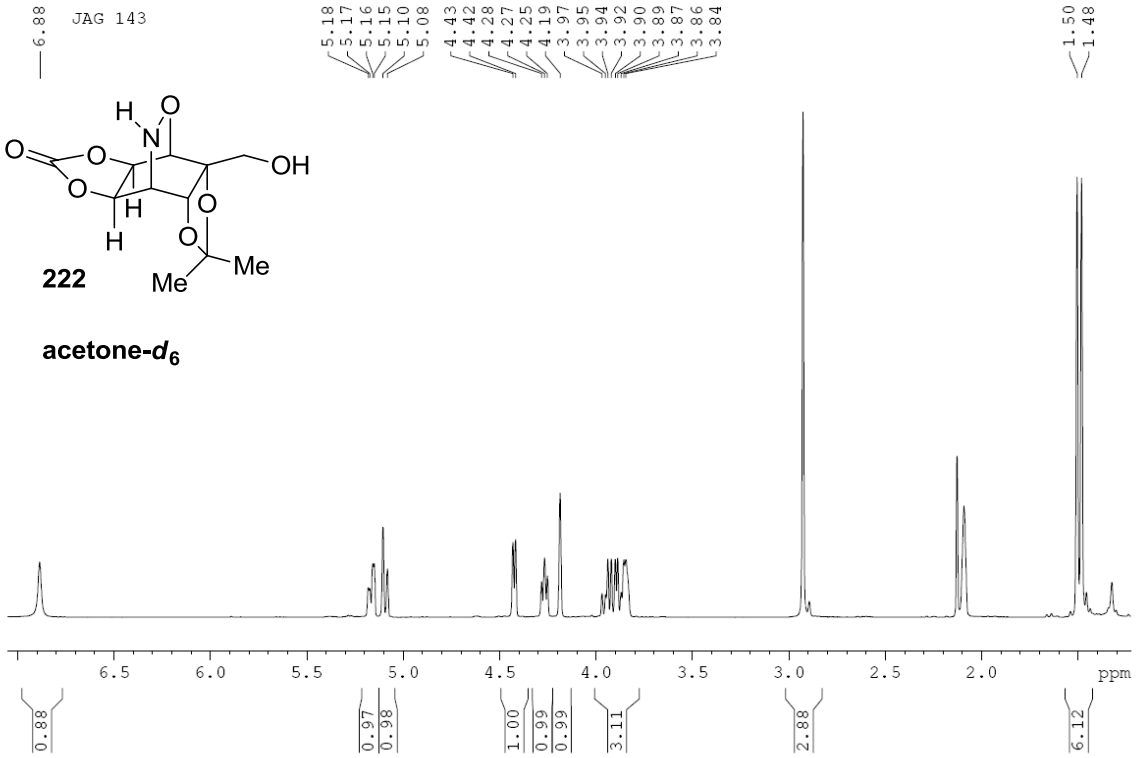
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5.08
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4.42
4.28
4.27
4.25
4.19
3.97
3.95
3.94
3.92
3.90
3.89
3.87
3.86
3.84
1.50
1.48
222
acetone-d6
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
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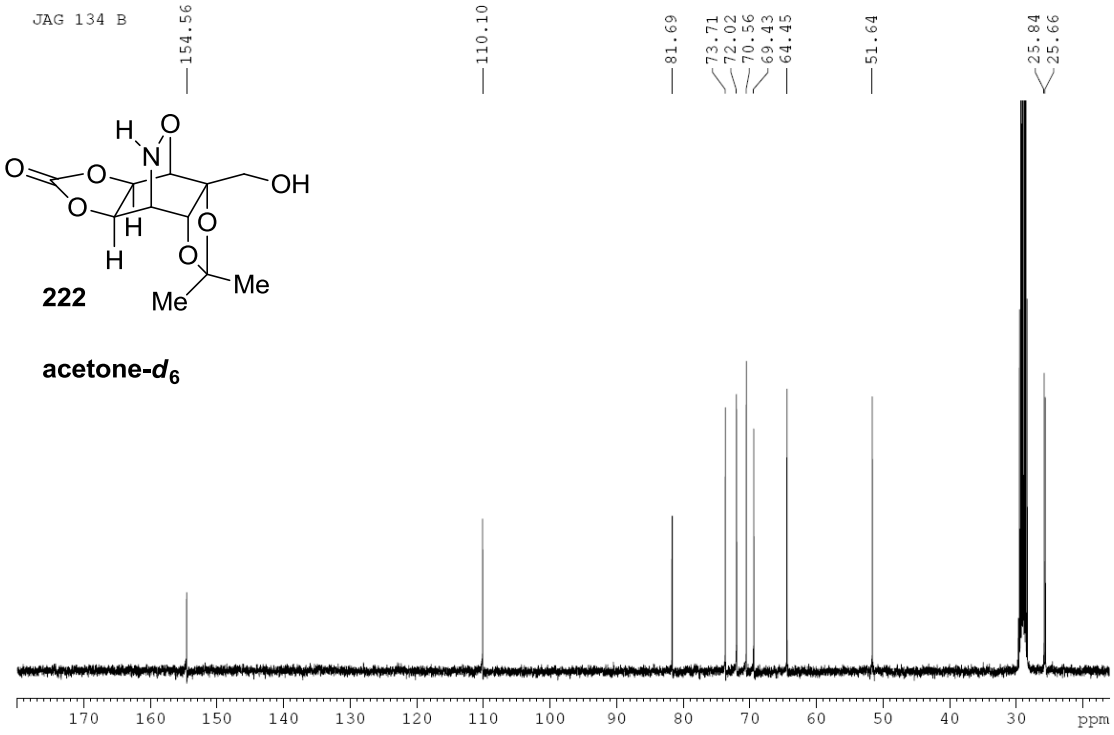
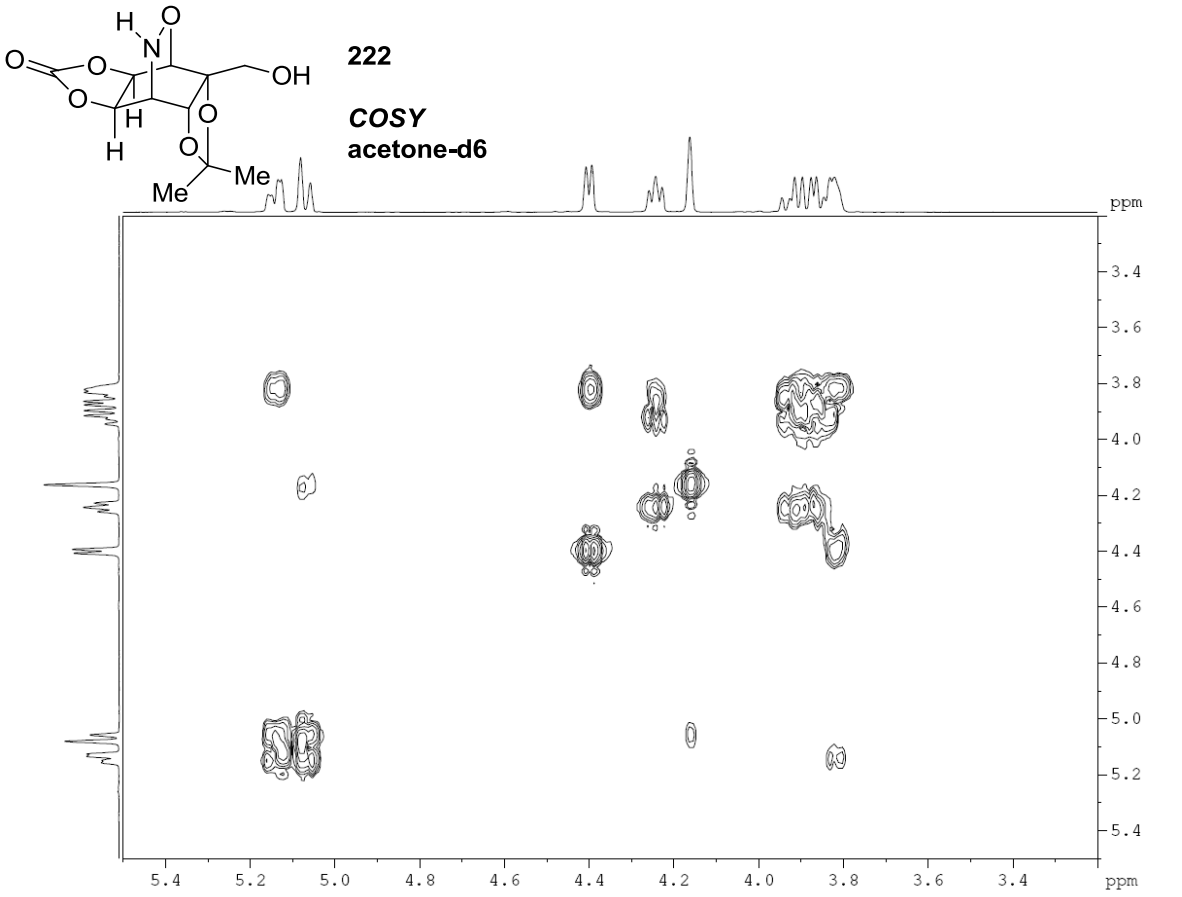
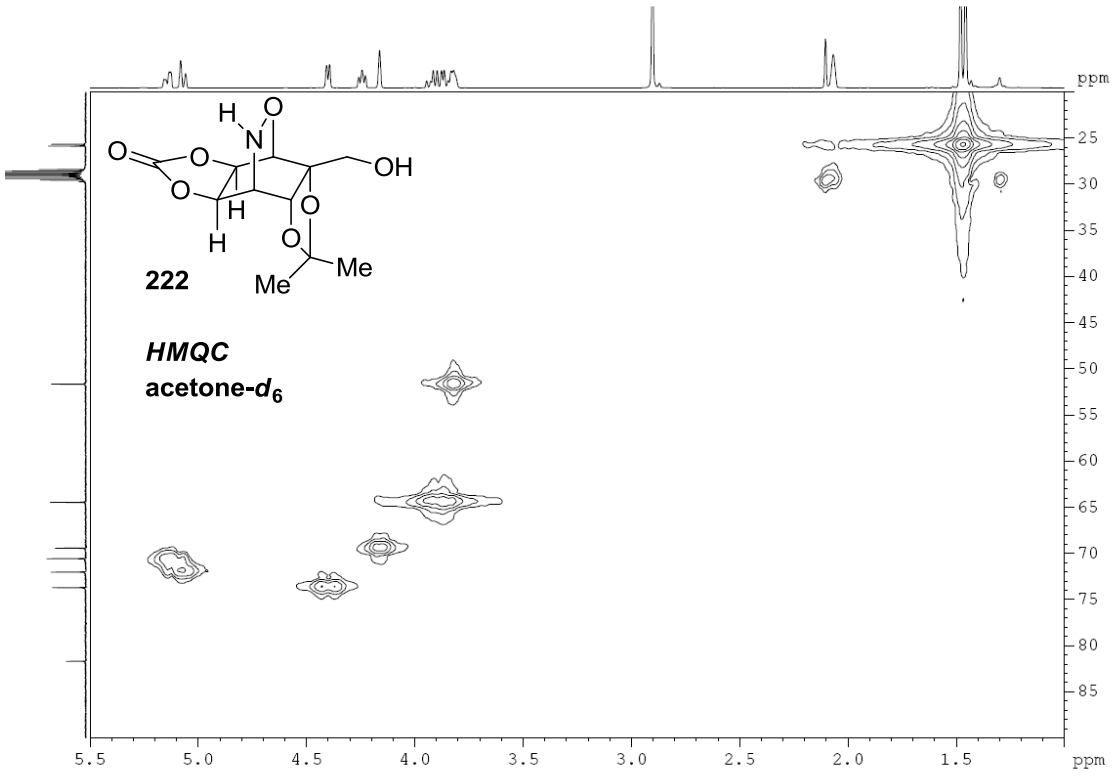
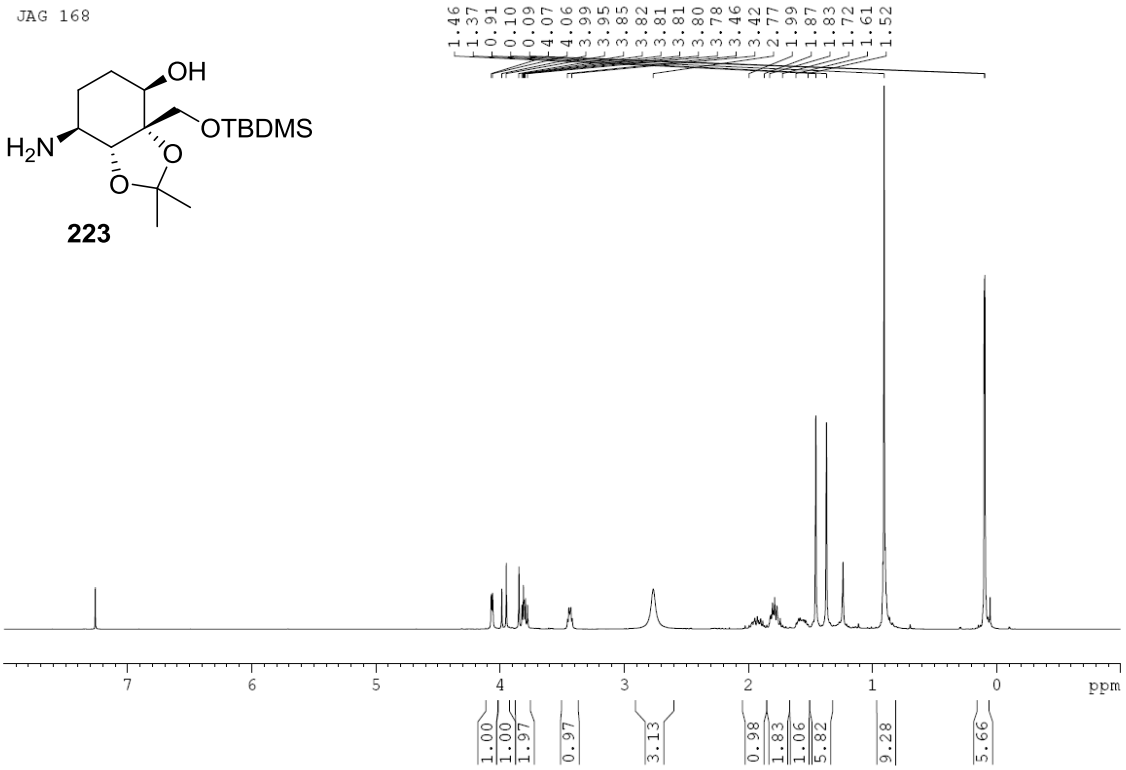
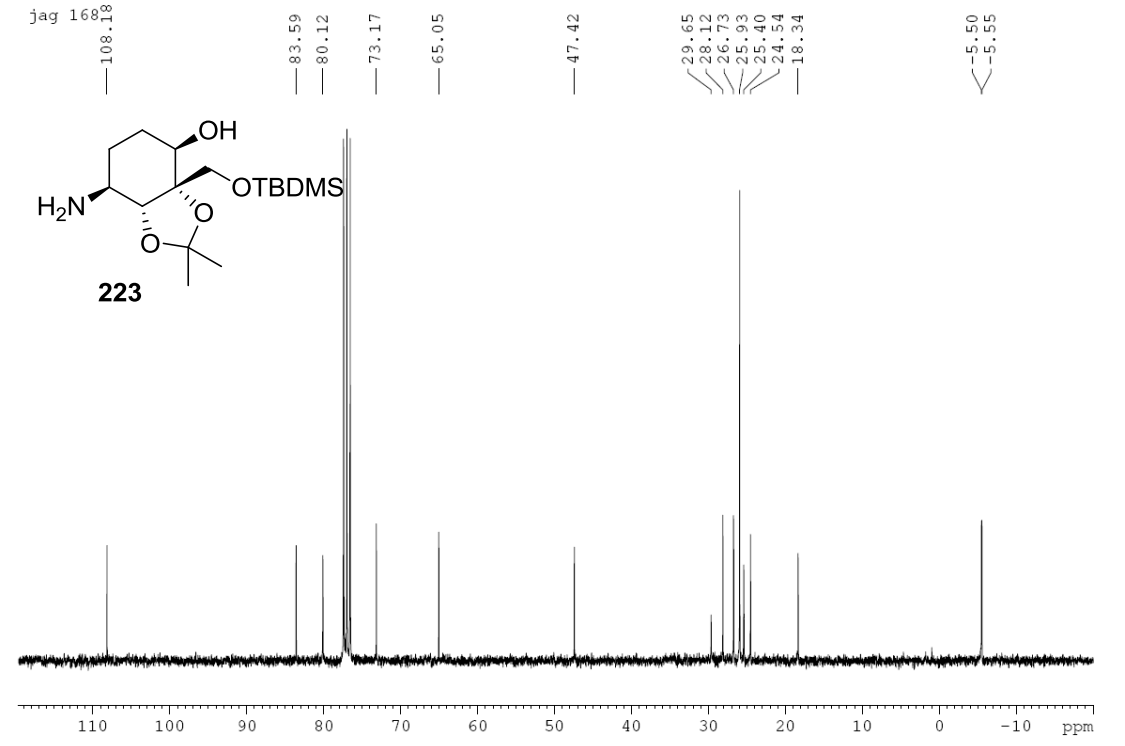
0.97
0.98
1.00
0.99
0.99
3.11
2.88
6.12

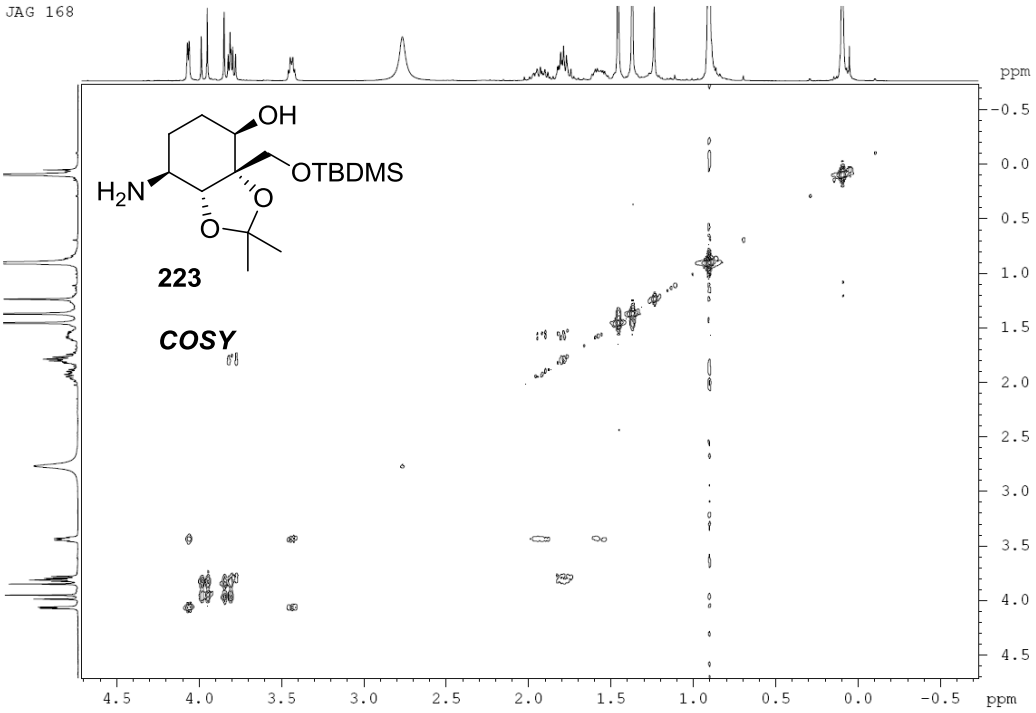

JAG 134 B
154.56
110.10
81.69
73.71
72.02
70.56
69.43
64.45
51.64
25.84
25.66
222
acetone-d6
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

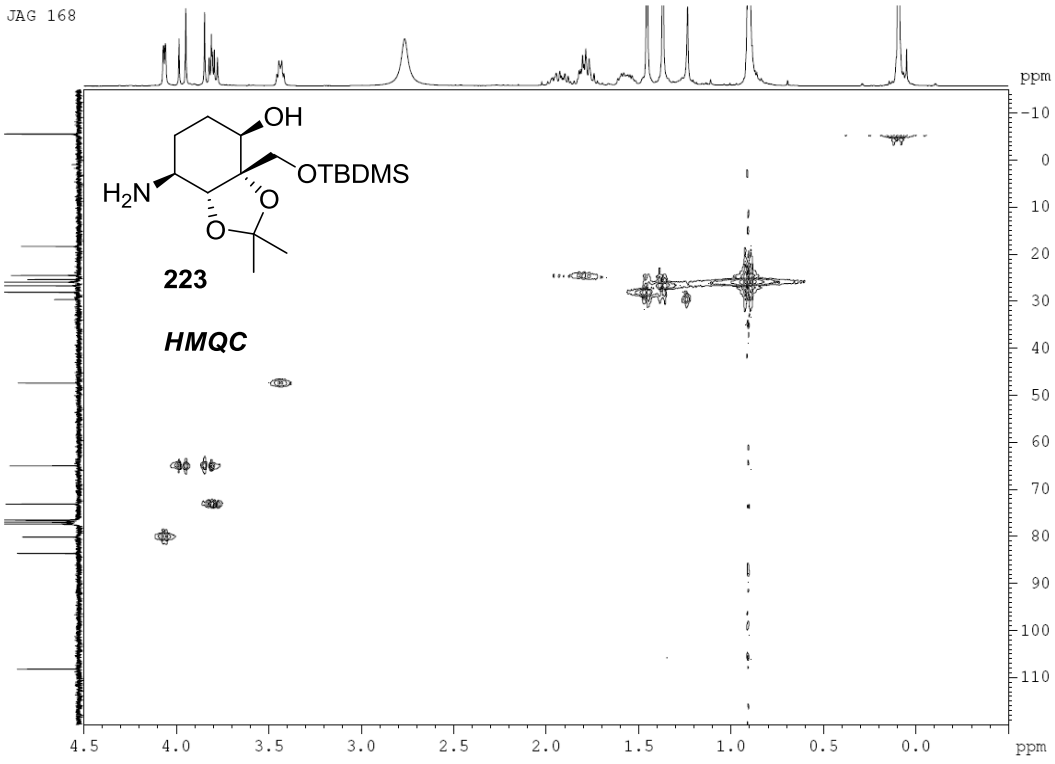

222
COSY
acetone-d6
ppm
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4
ppm

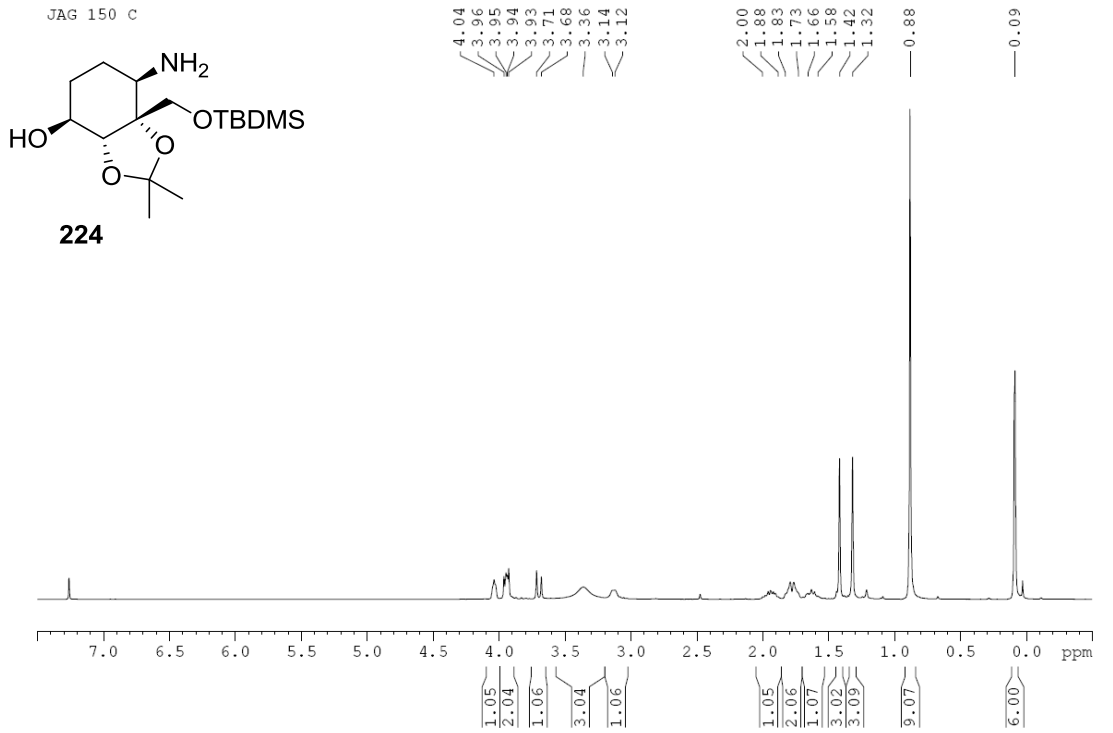

222
HMQC
acetone-d6
ppm
25
30
35
40
45
50
55
60
65
70
75
80
85
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
ppm

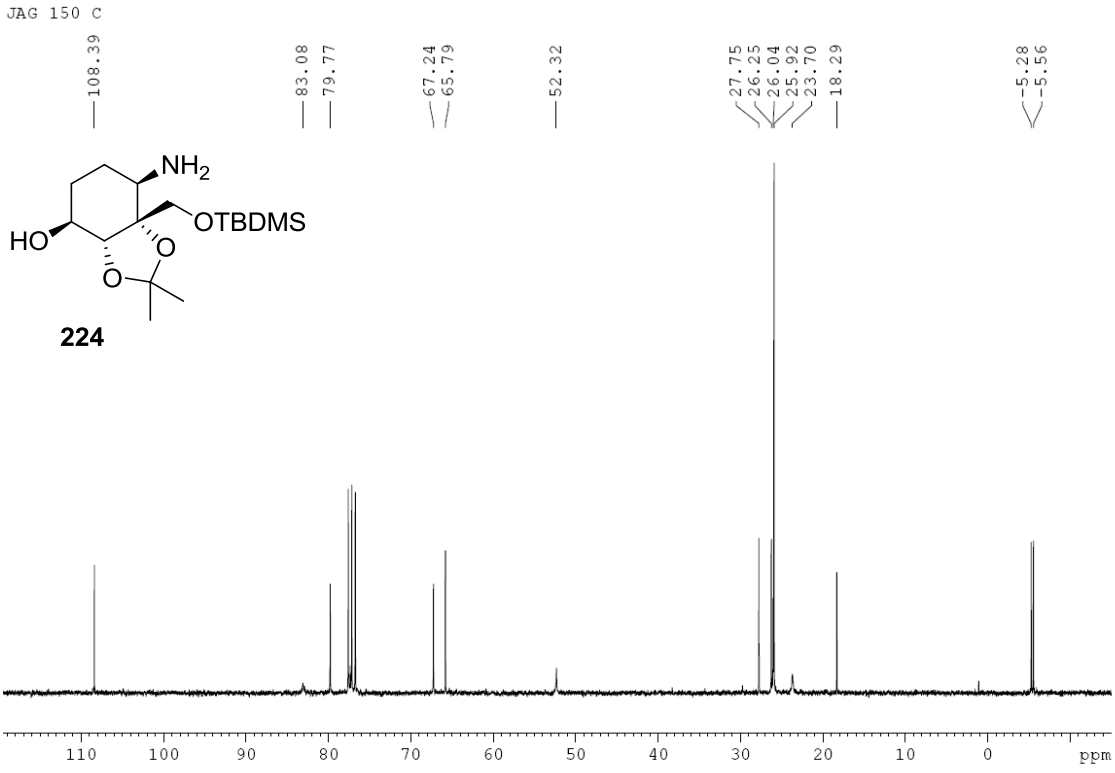

JAG 168
OH
H2N
OTBDMS
O
O
223
1.46
1.37
0.91
0.10
0.09
4.07
4.06
3.99
3.95
3.85
3.82
3.81
3.81
3.80
3.78
3.46
3.42
2.77
1.99
1.87
1.83
1.72
1.61
1.52
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.97
0.97
3.13
0.98
1.83
1.06
5.82
9.28
5.66

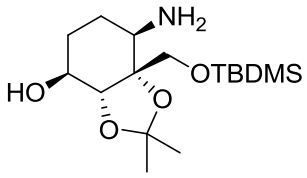

jag 168
108.18
83.59
80.12
73.17
65.05
47.42
29.65
28.12
26.73
25.93
25.40
24.54
18.34
-5.50
-5.55
OH
H2N
OTBDMS
O
O
223
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


JAG 168
OH
OTBDMS
H_2N
O
O
223
COSY
ppm
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
-0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5


JAG 168
OH
OTBDMS
H_2N
O
O
223
HMQC
ppm
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
-10 0 10 20 30 40 50 60 70 80 90 100 110

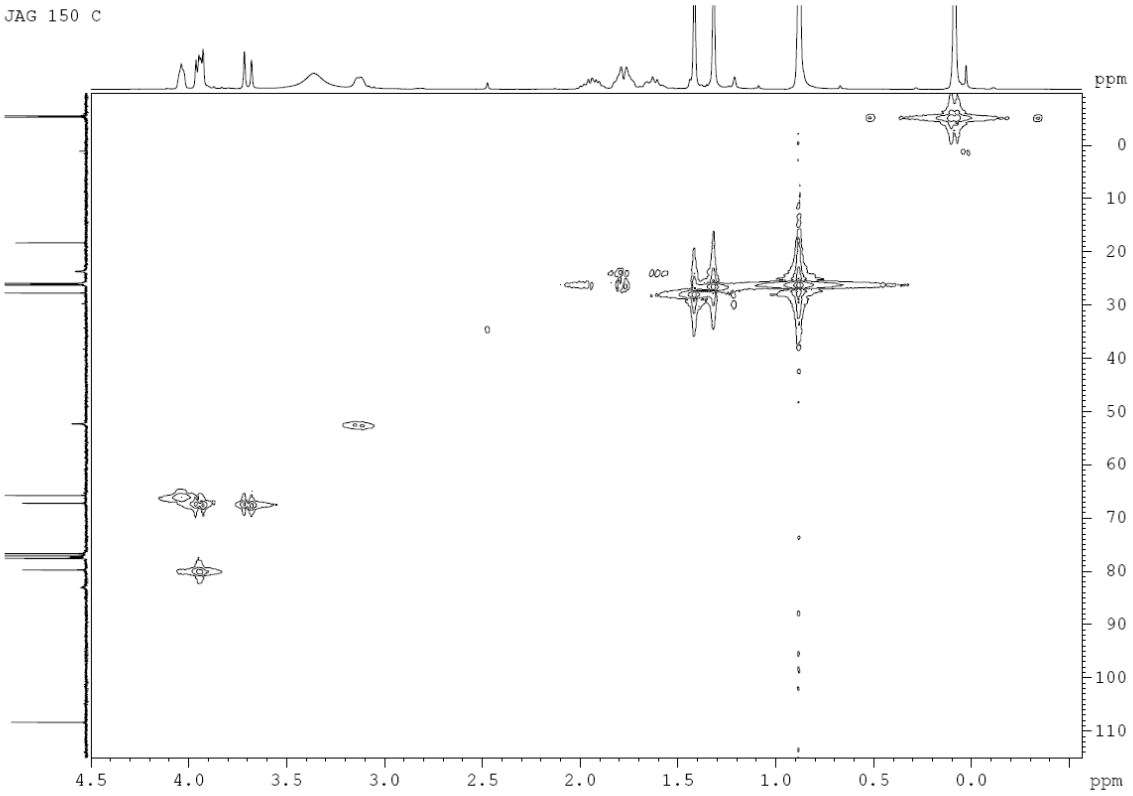

JAG 150 C
NH2
OTBDMS
HO
O
O
224
4.04
3.96
3.95
3.94
3.93
3.71
3.68
3.36
3.14
3.12
2.00
1.88
1.83
1.73
1.66
1.58
1.42
1.32
0.88
0.09
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.05
2.04
1.06
3.04
1.06
1.05
2.06
1.07
3.02
3.09
9.07
6.00

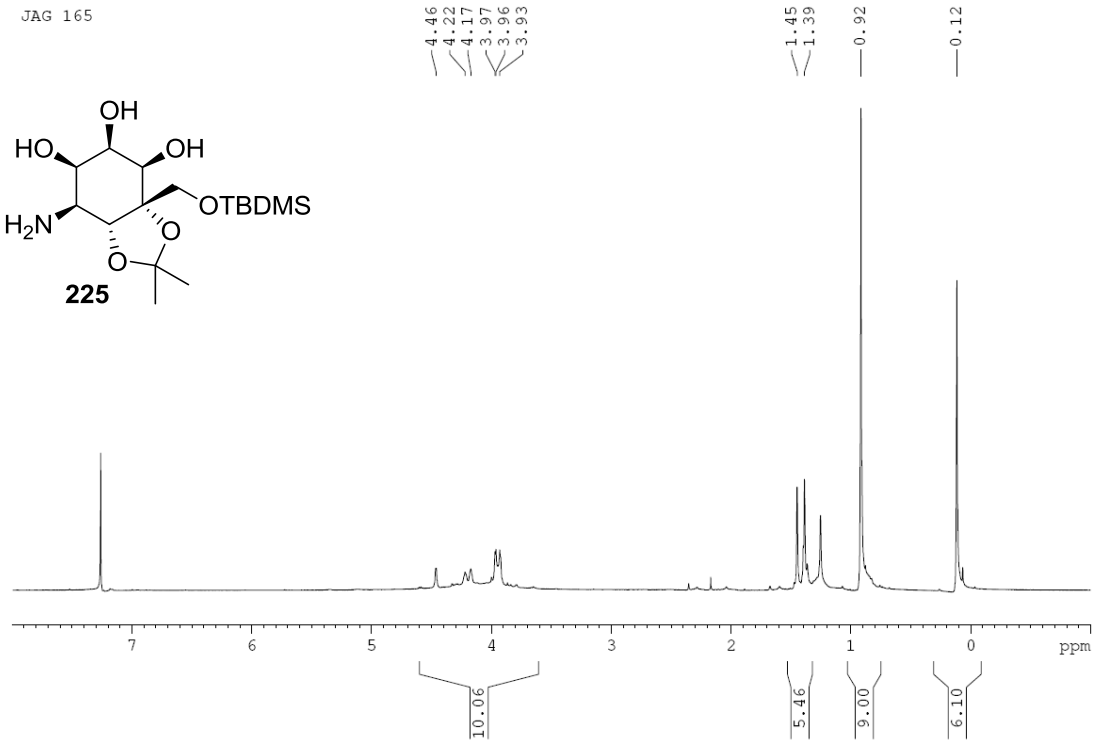

JAG 150 C
108.39
83.08
79.77
67.24
65.79
52.32
27.75
26.25
26.04
25.92
23.70
18.29
-5.28
-5.56
NH2
OTBDMS
HO
O
O
224
110
100
90
80
70
60
50
40
30
20
10
0
ppm

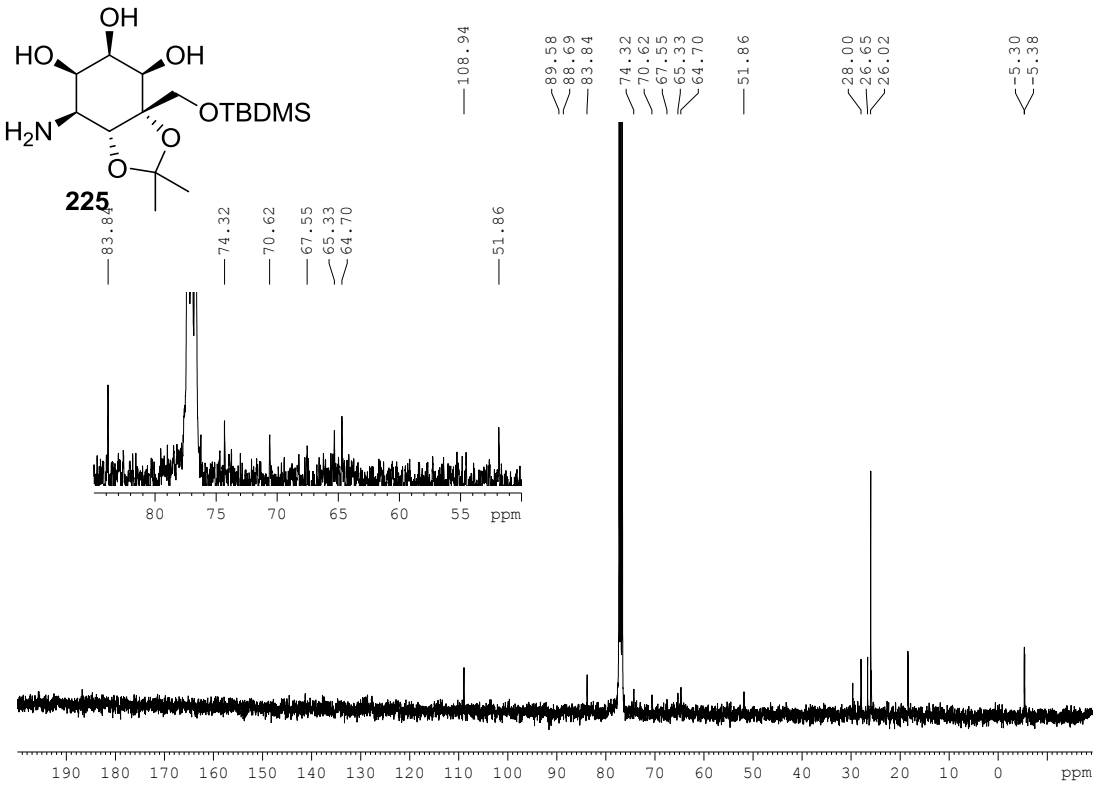

NH2
OTBDMS
HO
O
O

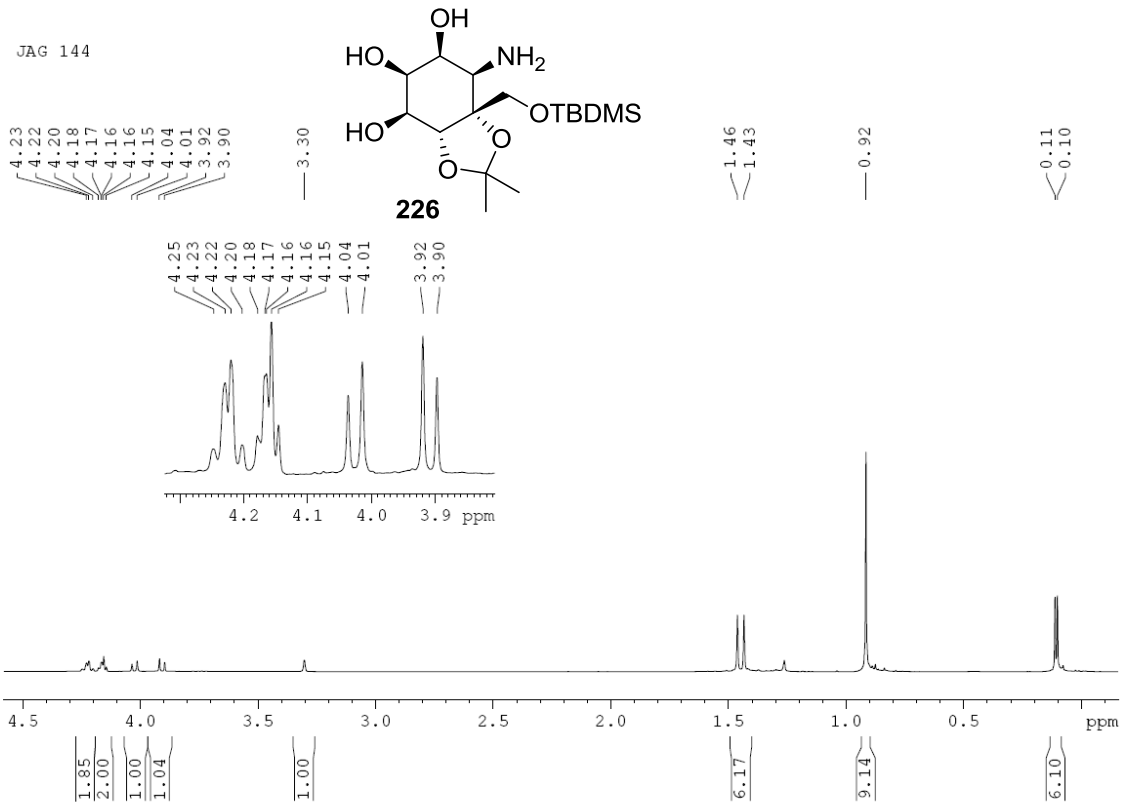
224

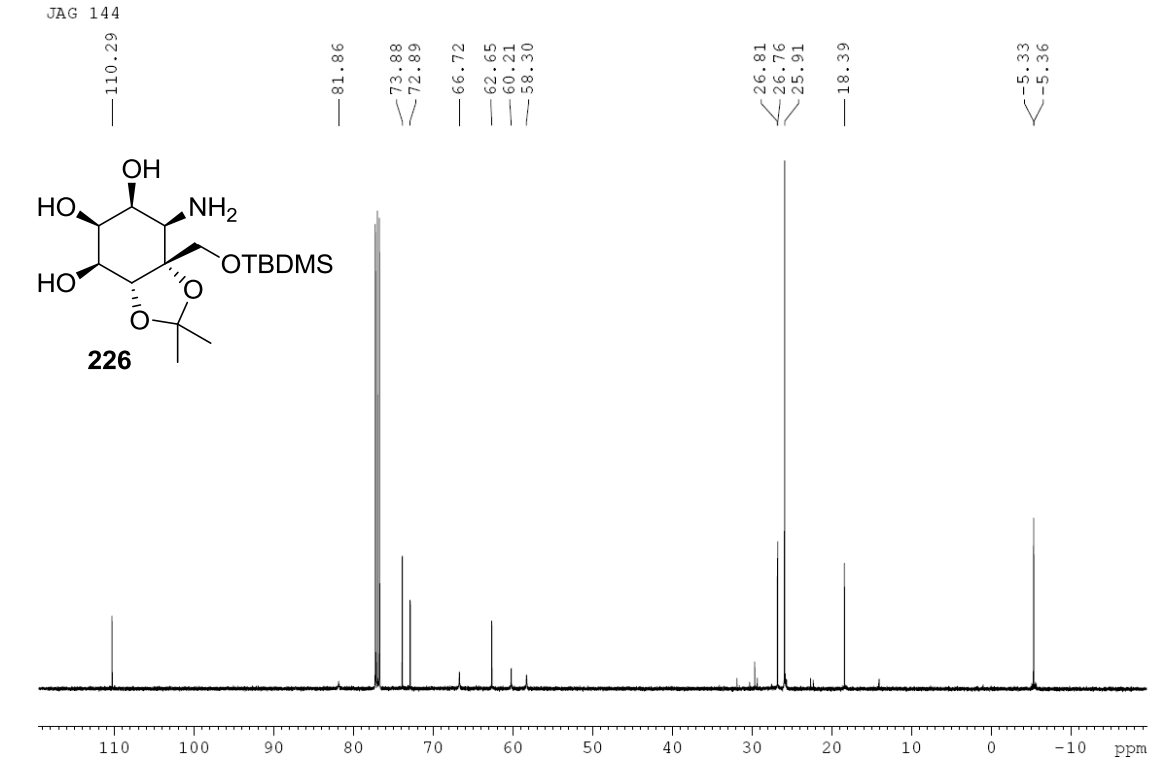
HMQC

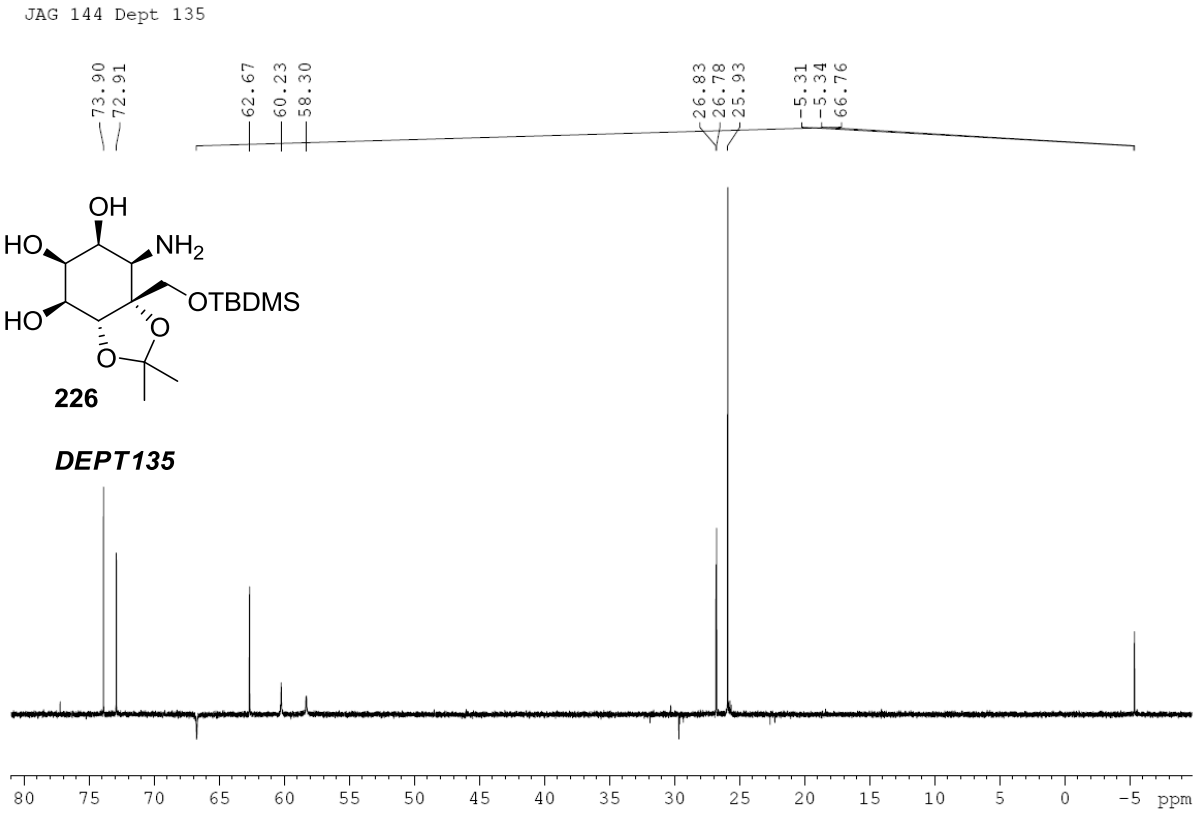

JAG 150 C
ppm
0
10
20
30
40
50
60
70
80
90
100
110
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

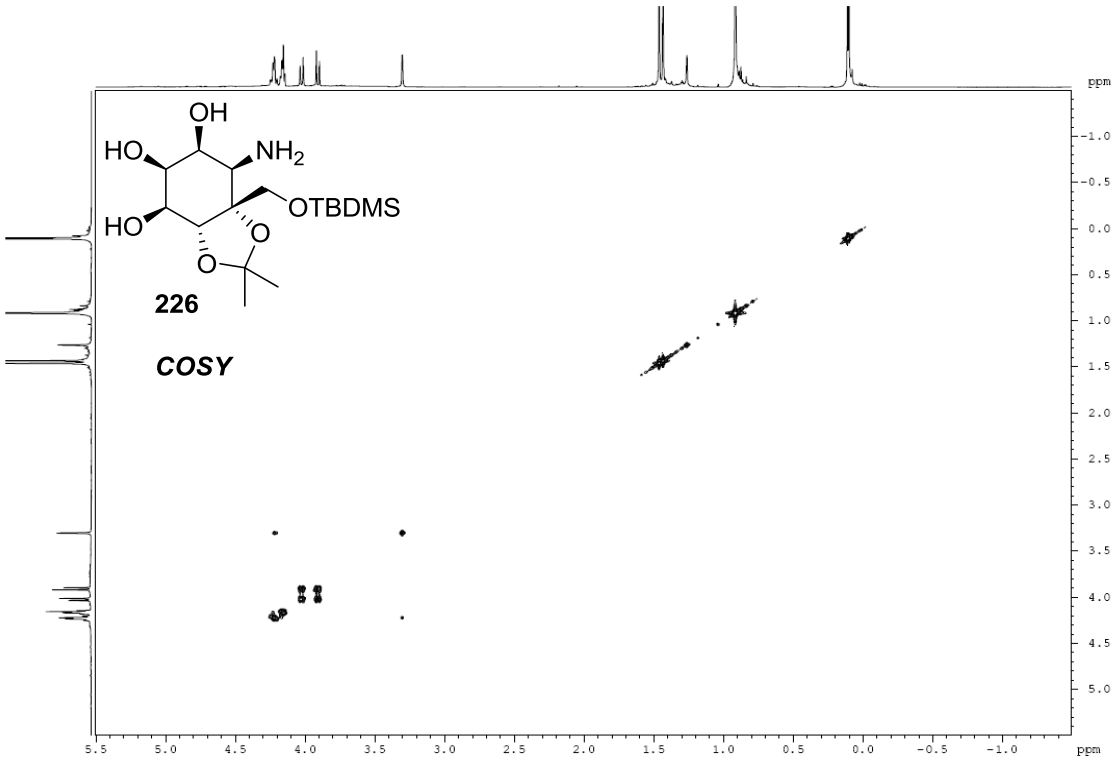

JAG 165
4.46
4.22
4.17
3.97
3.96
3.93
1.45
1.39
0.92
0.12
OH
HO
OH
OTBDMS
H_2N
O
O
225
7
6
5
4
3
2
1
0
ppm
10.06
5.46
9.00
6.10

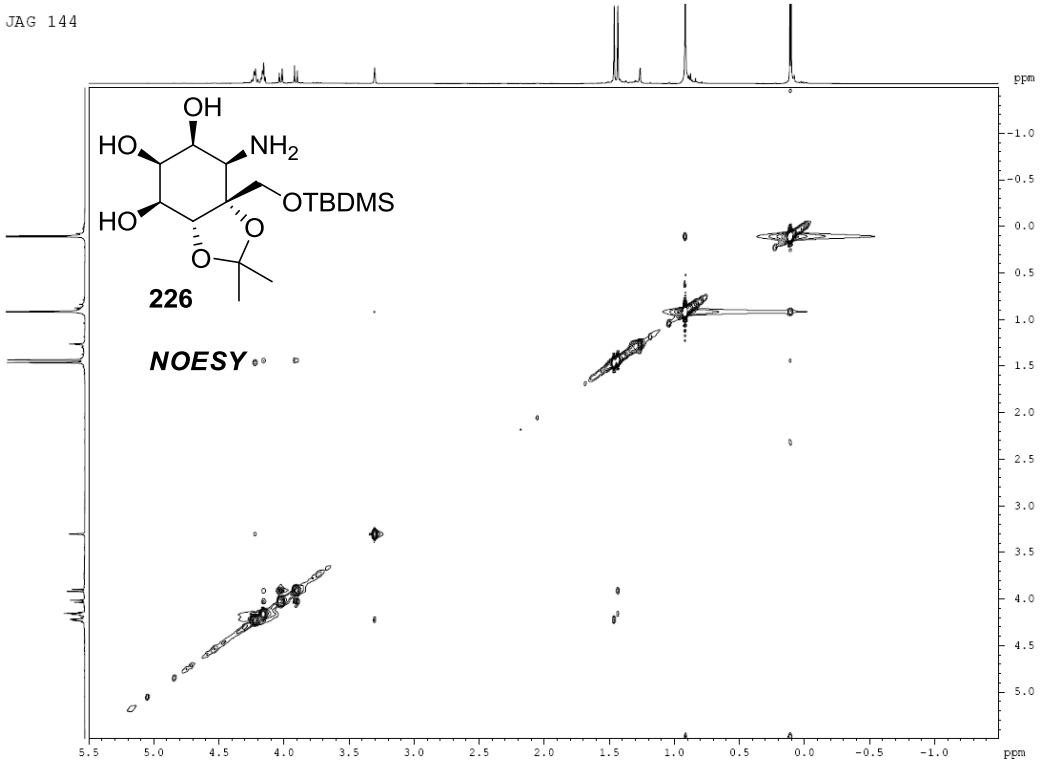

OH
HO
OH
OTBDMS
H_2N
O
O
225
108.94
89.58
88.69
83.84
74.32
70.62
67.55
65.33
64.70
51.86
28.00
26.65
26.02
5.30
5.38
83.84
74.32
70.62
67.55
65.33
64.70
51.86
80
75
70
65
60
55
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

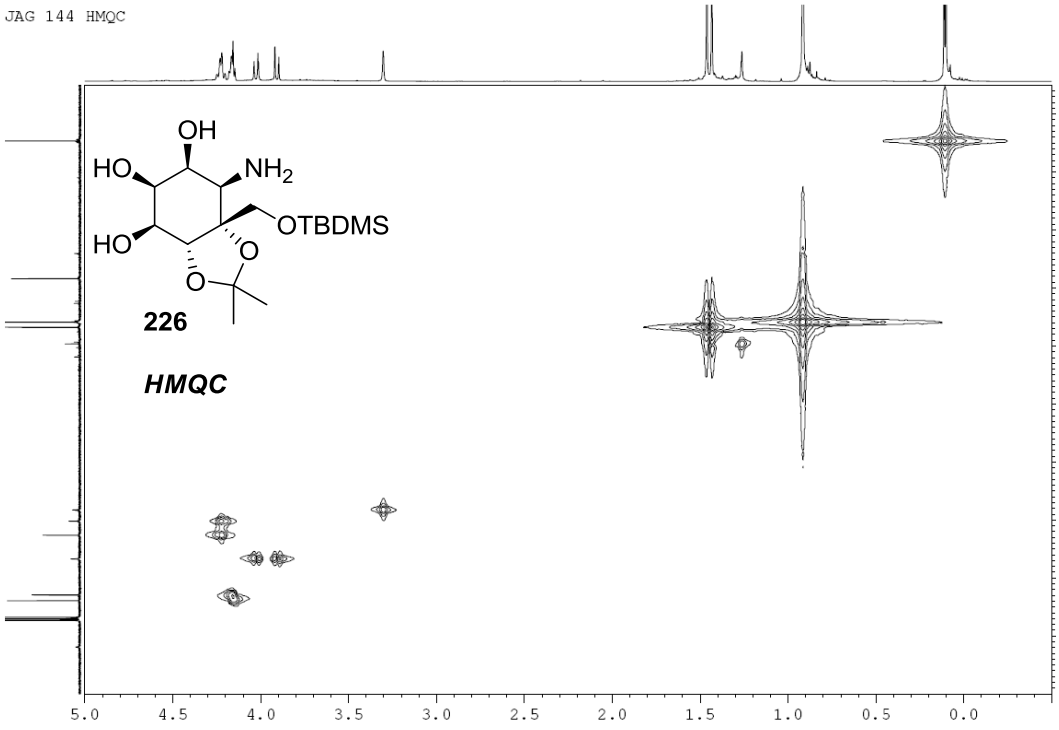

JAG 144
OH
HO
NH2
OTBDMS
HO
O
O
226
4.23
4.22
4.20
4.18
4.17
4.16
4.16
4.15
4.04
4.01
3.92
3.90
3.30
1.46
1.43
0.92
0.11
0.10
4.25
4.23
4.22
4.20
4.18
4.17
4.16
4.16
4.15
4.04
4.01
3.92
3.90
4.2
4.1
4.0
3.9 ppm
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.85
2.00
1.00
1.04
1.00
6.17
9.14
6.10

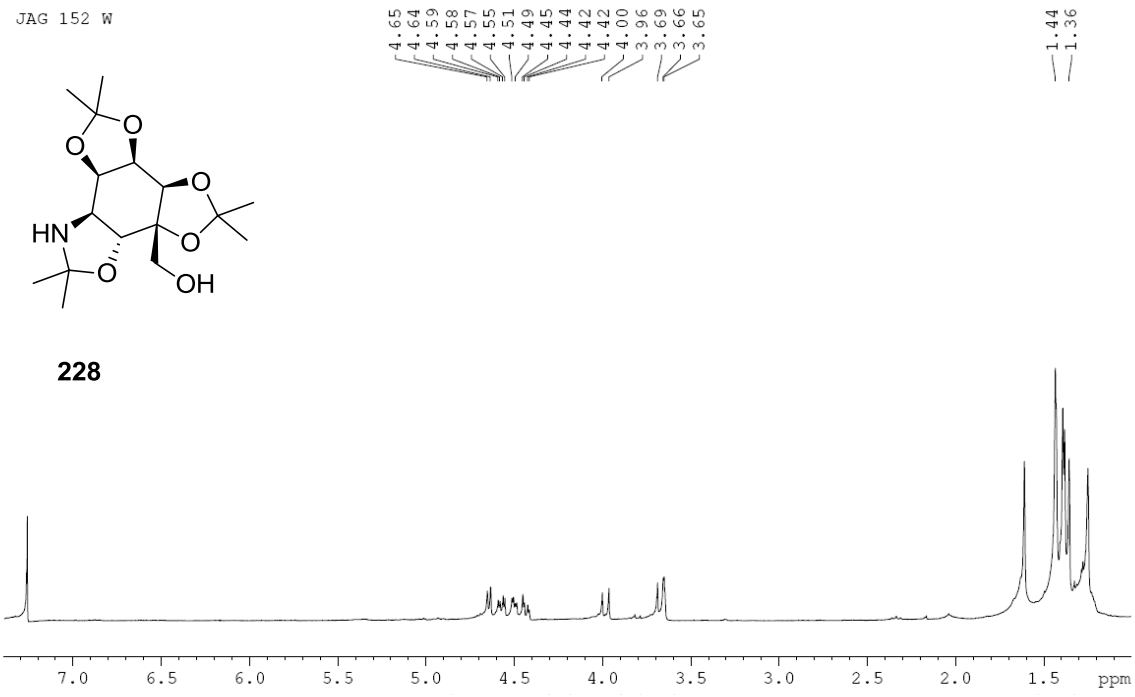

JAG 144
110.29
81.86
73.88
72.89
66.72
62.65
60.21
58.30
26.81
26.76
25.91
18.39
5.33
5.36
OH
HO
NH2
OTBDMS
HO
O
O
226
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


JAG 144 Dept 135
73.90
72.91
62.67
60.23
58.30
26.83
26.78
25.93
-5.31
-5.34
66.76
OH
HO
NH2
OTBDMS
HO
O
O
226
DEPT135
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 ppm

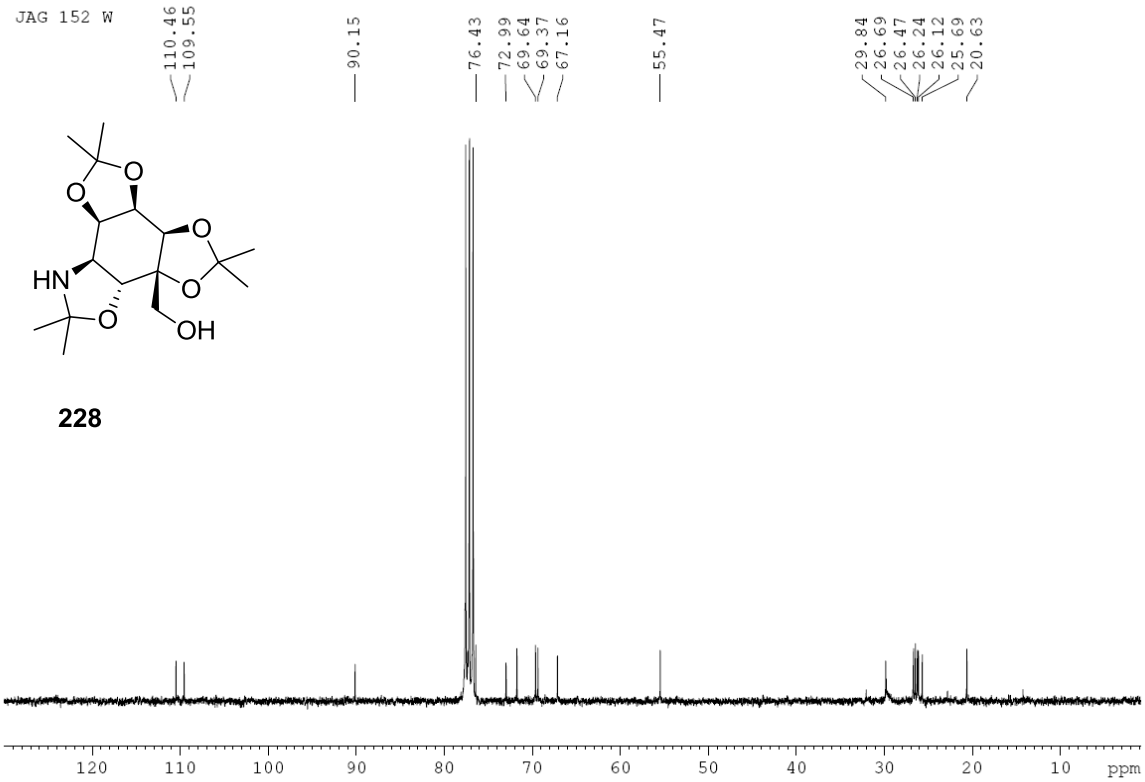

OH
HO
NH2
OTBDMS
HO
O
O
226
COSY
ppm
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 ppm


JAG 144
OH
HO
NH2
OTBDMS
HO
O
O
226
NOESY
ppm
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 ppm

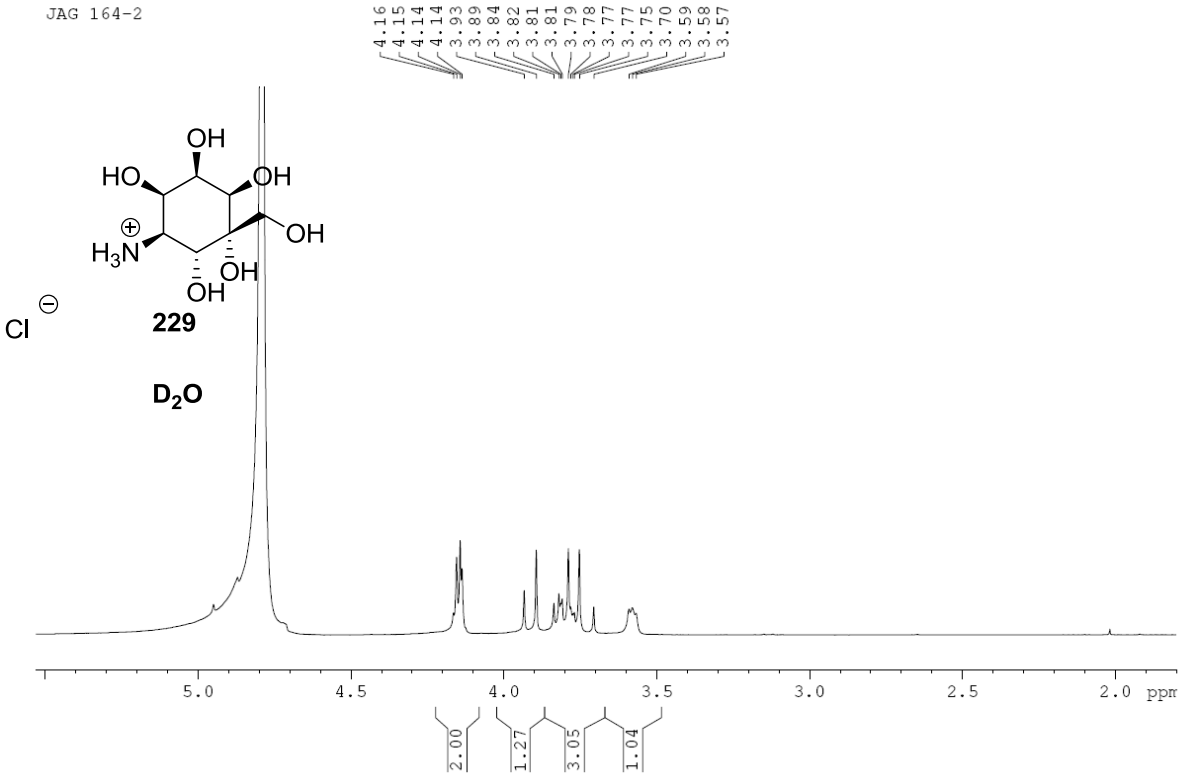

JAG 144 HMQC
OH
HO
NH2
OTBDMS
HO
O
O
226
HMQC
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

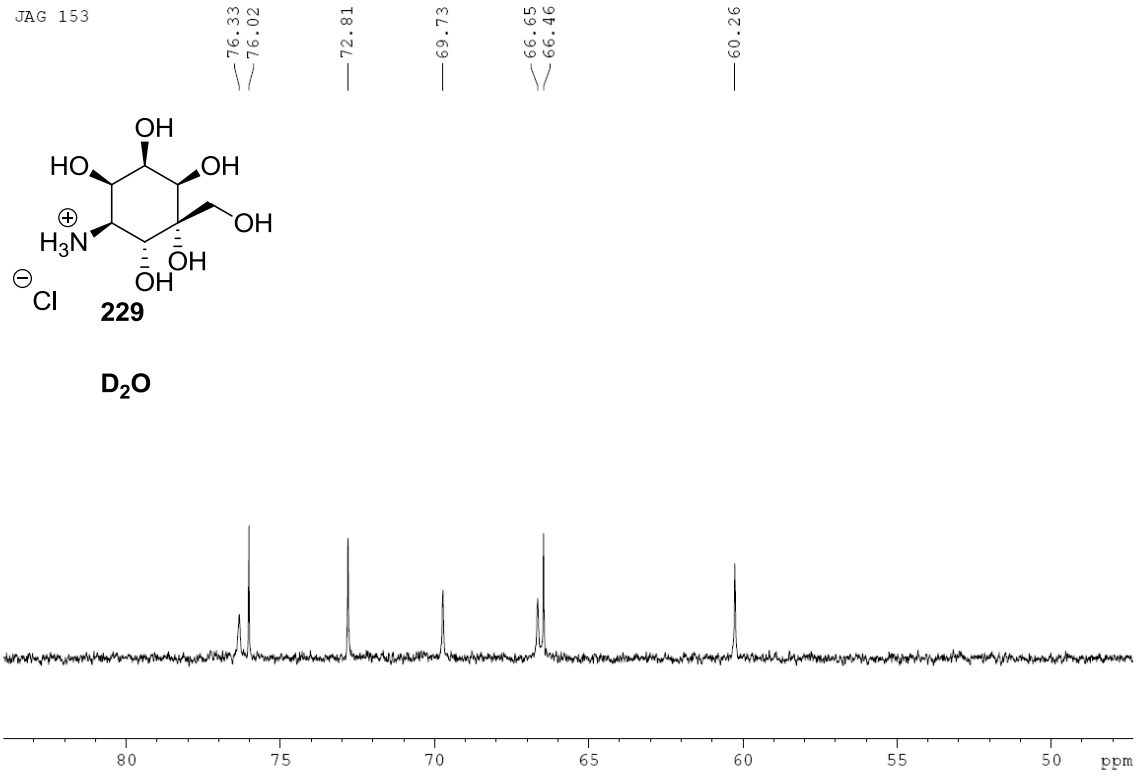

JAG 152 W
4.65
4.64
4.59
4.58
4.57
4.55
4.51
4.49
4.45
4.44
4.42
4.42
4.00
3.96
3.69
3.66
3.65
1.44
1.36
HN
O
O
O
O
O
O
OH
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

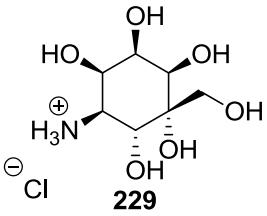
228


JAG 152 W
110.46
109.55
90.15
76.43
72.99
69.64
69.37
67.16
55.47
29.84
26.69
26.47
26.24
26.12
25.69
20.63
HN
O
O
O
O
O
O
OH
120
110
100
90
80
70
60
50
40
30
20
10
ppm

228


JAG 164-2
4.16
4.15
4.14
4.14
3.93
3.89
3.84
3.82
3.81
3.81
3.79
3.78
3.77
3.77
3.75
3.70
3.59
3.58
3.57
OH
HO
OH
OH
H3N
OH
OH
Cl
229
D2O
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
2.00
1.27
3.05
1.04

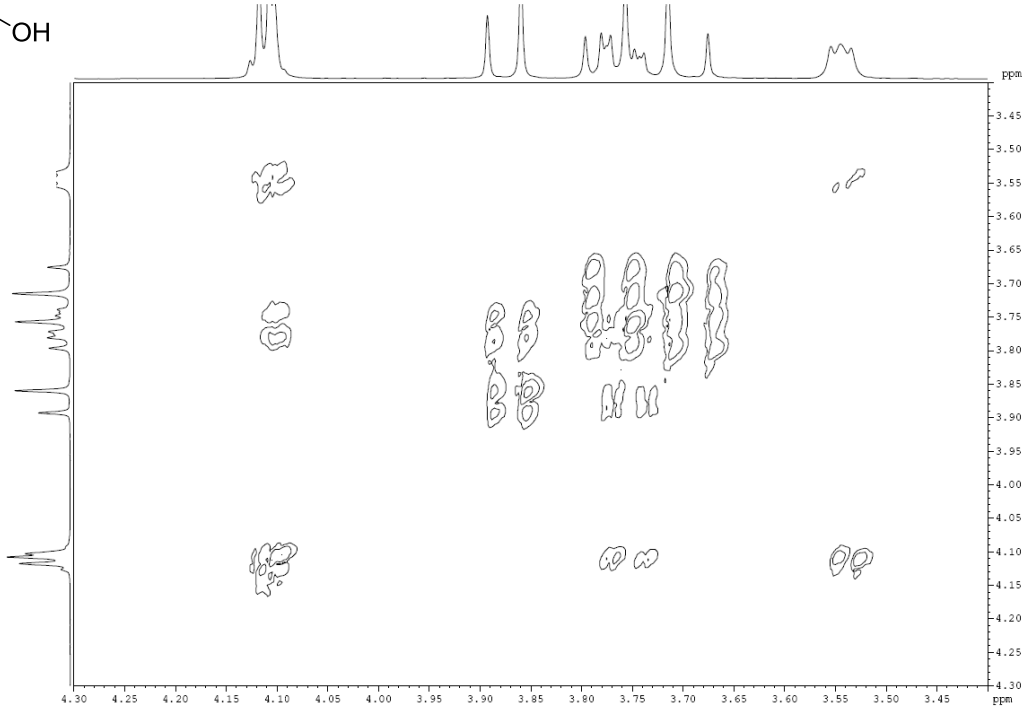

JAG 153
76.33
76.02
72.81
69.73
66.65
66.46
60.26
OH
HO
OH
OH
H3N
OH
OH
Cl
229
D2O
80
75
70
65
60
55
50
ppm

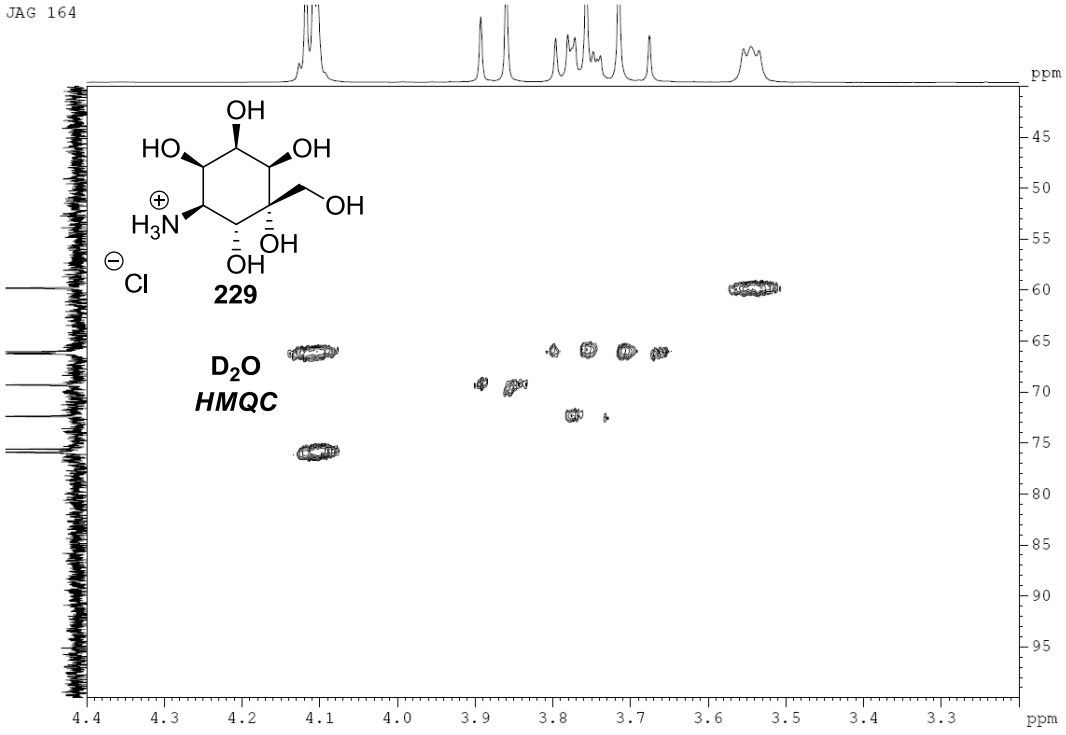


229

D_2O

COSY

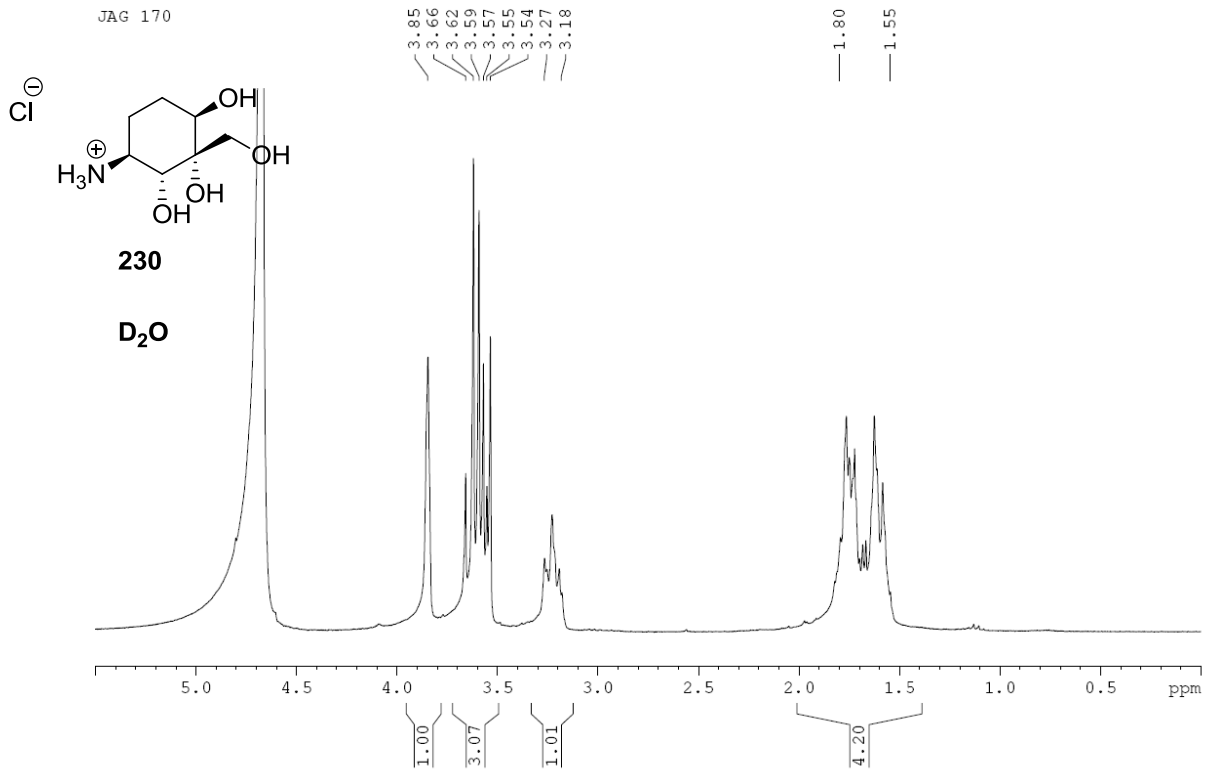


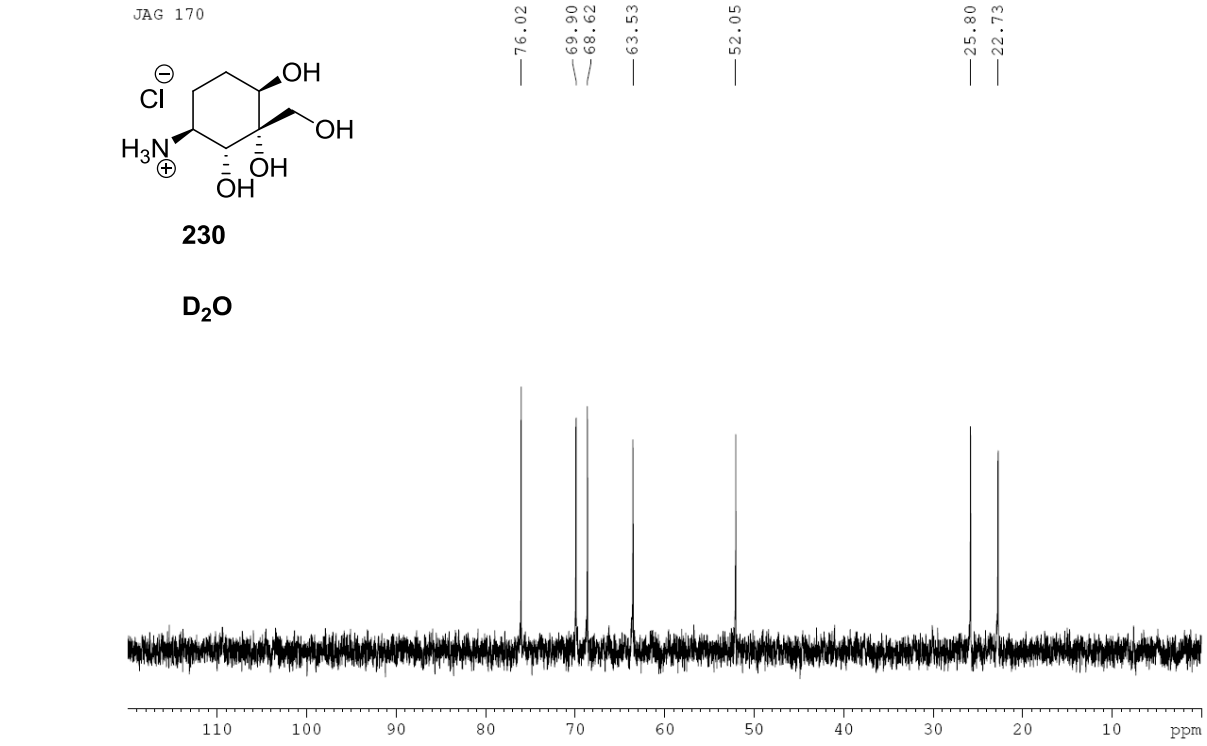


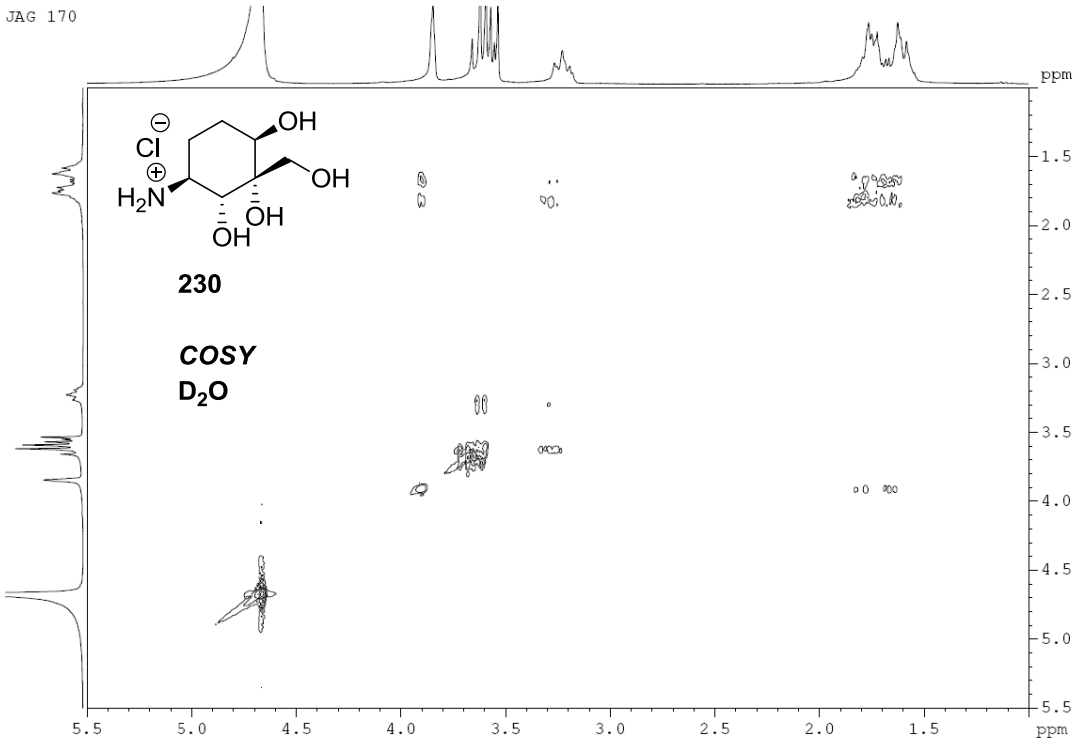
229

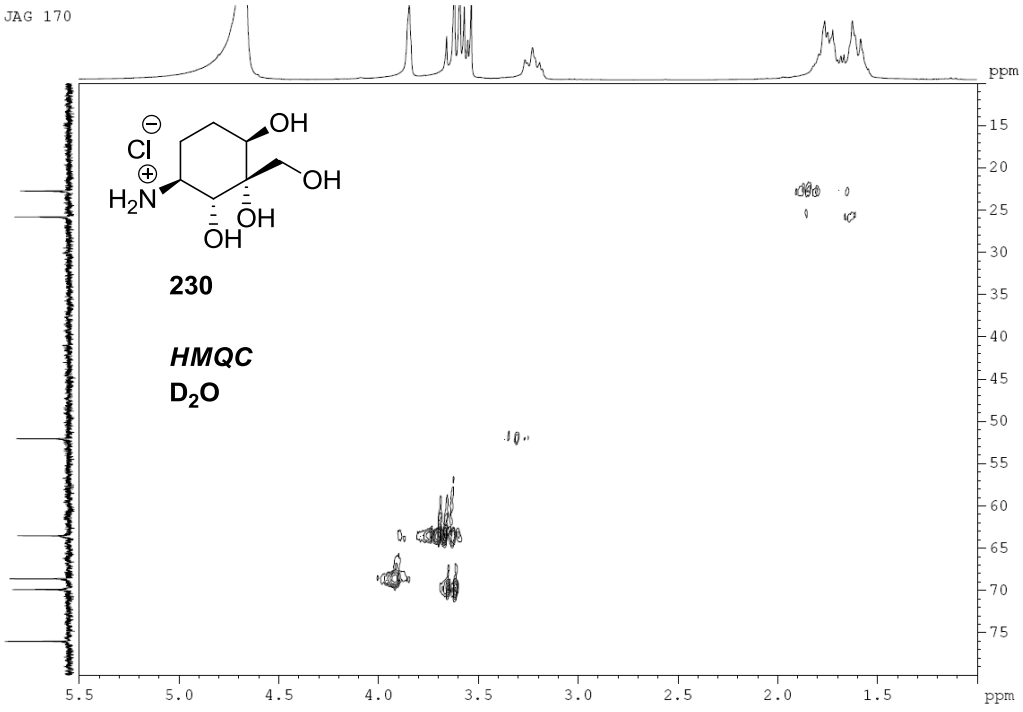
D_2O

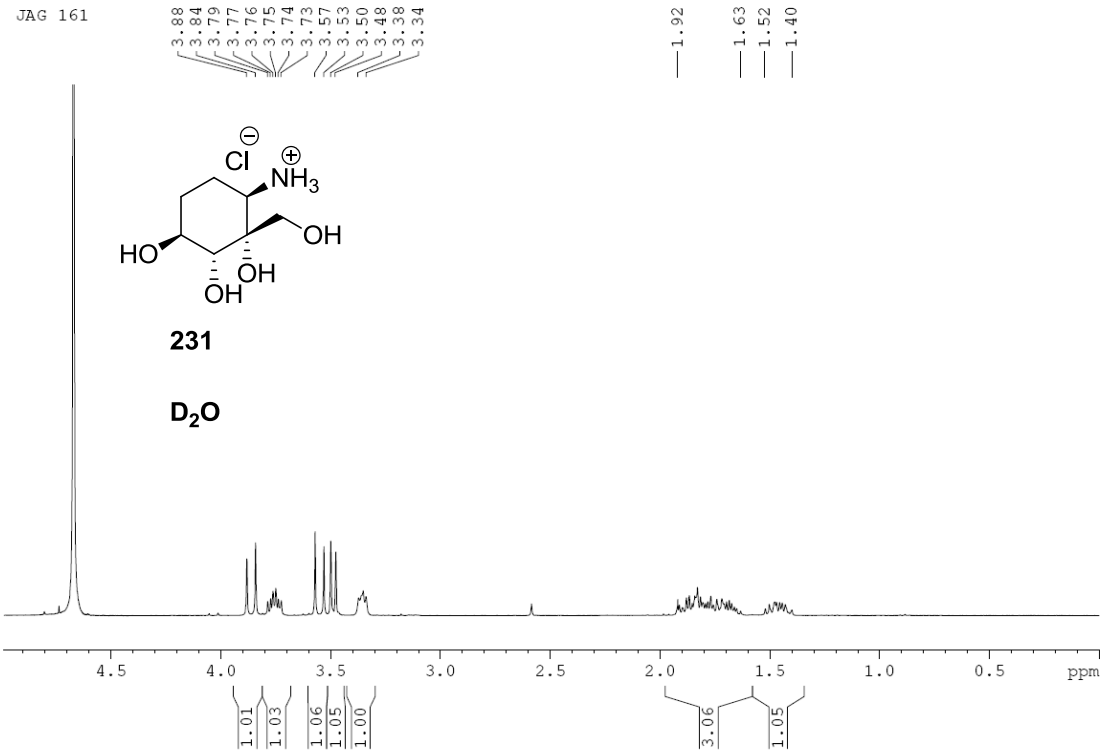
HMQC

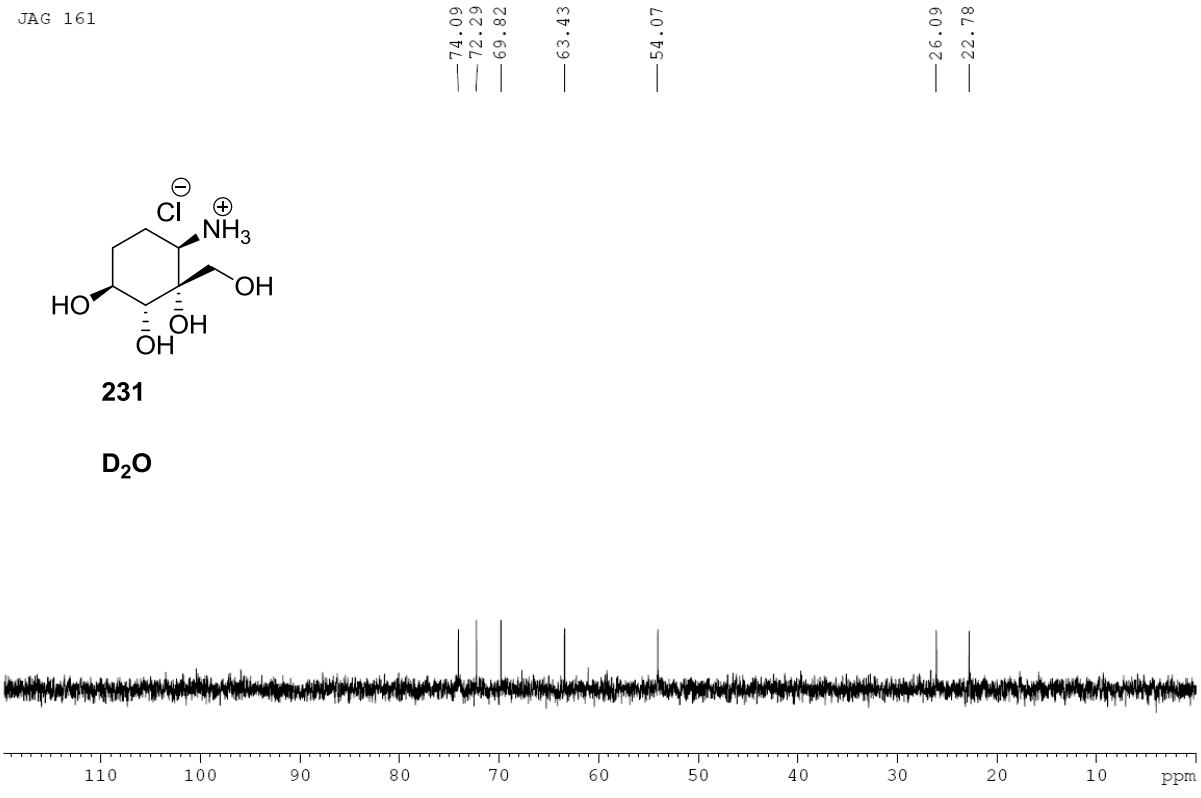

JAG 170
3.85
3.66
3.62
3.59
3.57
3.55
3.54
3.27
3.18
1.80
1.55
Cl
OH
OH
H3N
OH
OH
230
D2O
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
3.07
1.01
4.20

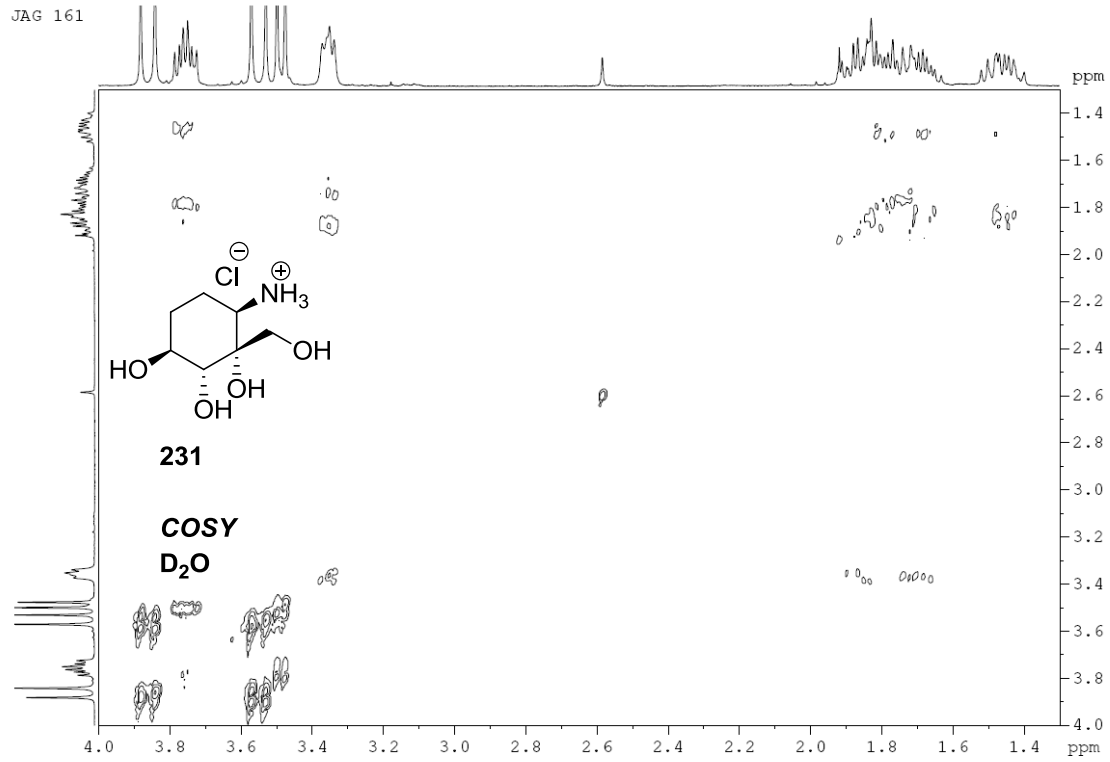

JAG 170
76.02
69.90
68.62
63.53
52.05
25.80
22.73
Cl
OH
OH
H3N
OH
OH
230
D2O
110
100
90
80
70
60
50
40
30
20
10
ppm

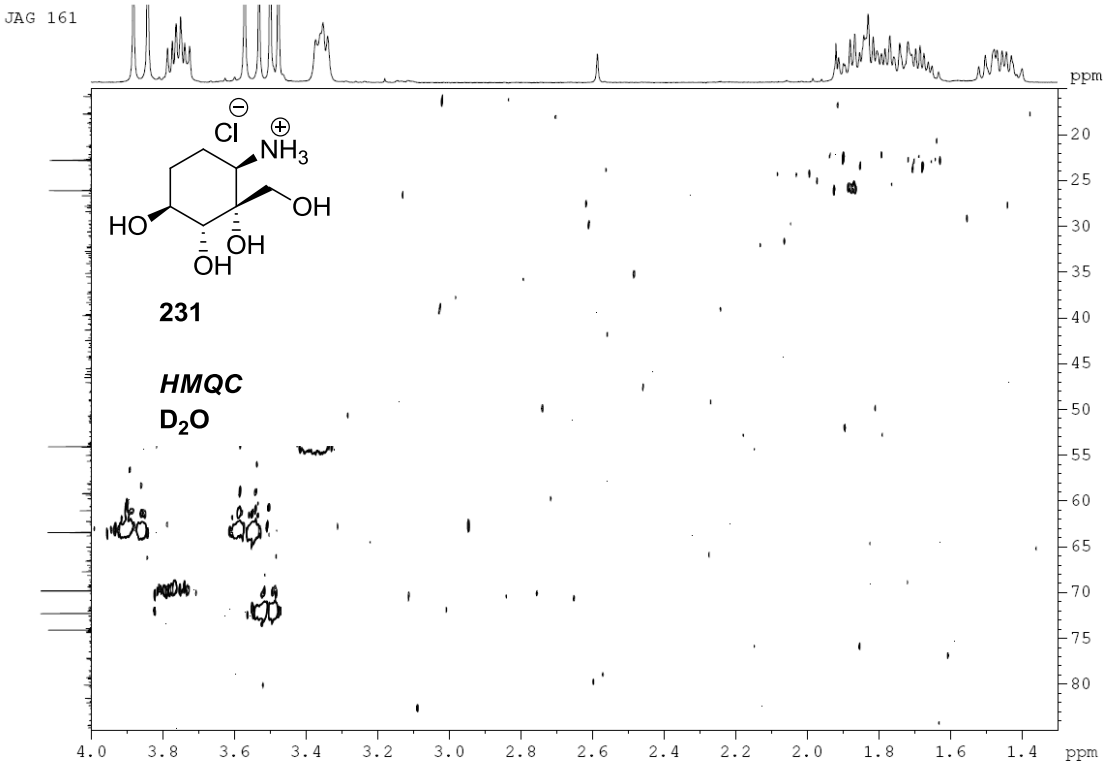

JAG 170
OH
Cl
OH
H2N
OH
OH
230
COSY
D2O
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

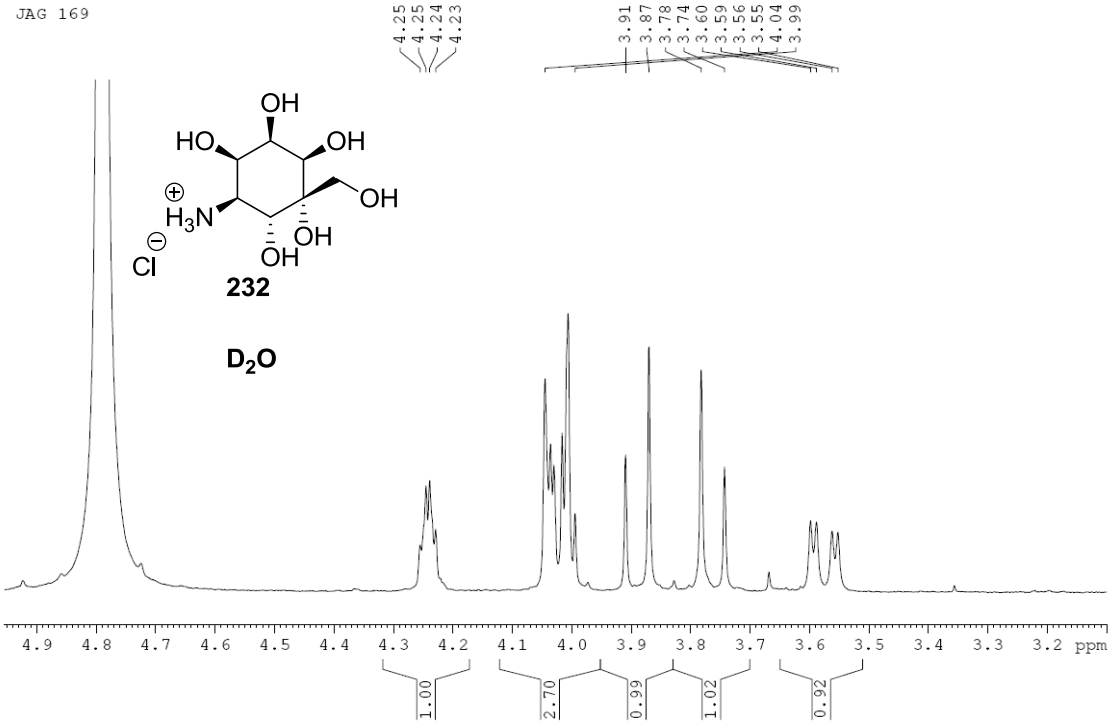

JAG 170
OH
Cl
OH
H2N
OH
OH
230
HMQC
D2O
ppm
15
20
25
30
35
40
45
50
55
60
65
70
75
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

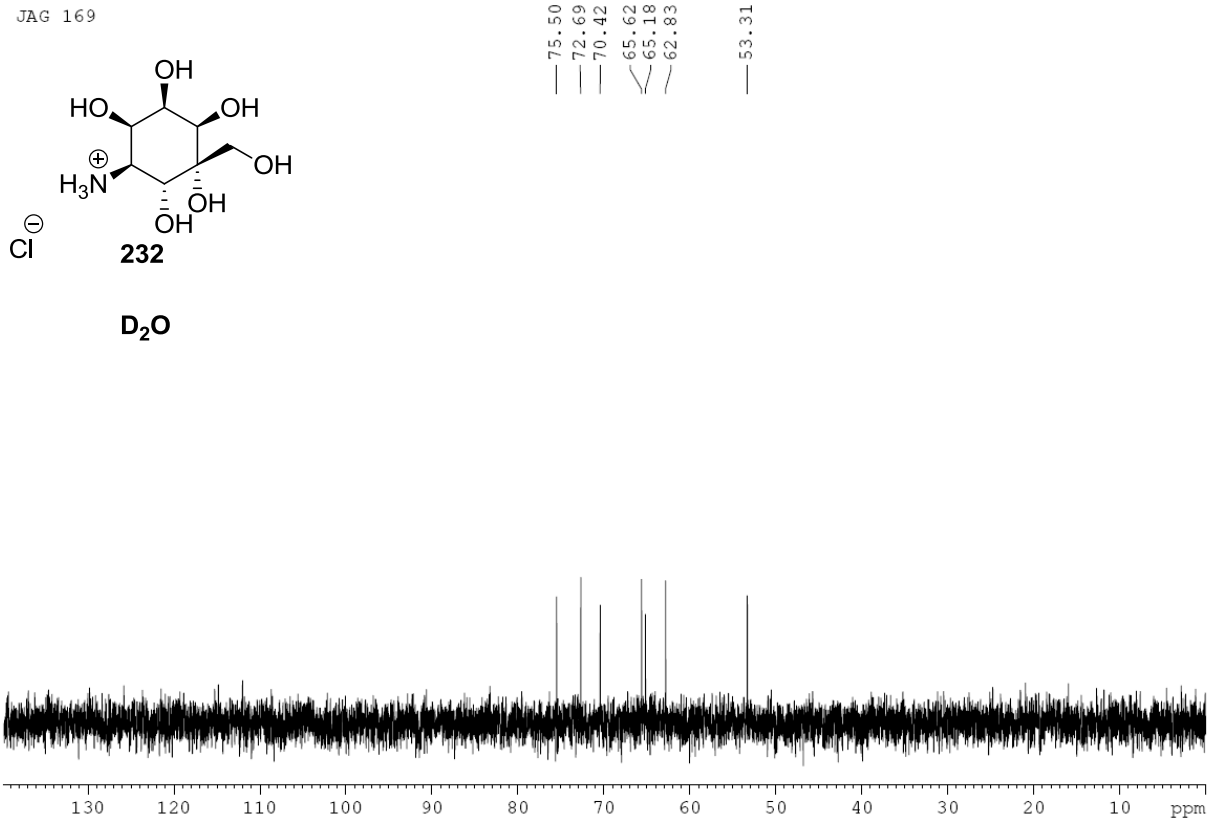

JAG 161
3.88
3.84
3.79
3.77
3.76
3.75
3.74
3.73
3.57
3.53
3.50
3.48
3.38
3.34
1.92
1.63
1.52
1.40
Cl
NH3
HO
OH
OH
OH
231
D2O
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.01
1.03
1.06
1.05
1.00
3.06
1.05

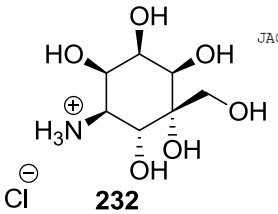

JAG 161
74.09
72.29
69.82
63.43
54.07
26.09
22.78
Cl
NH3
HO
OH
OH
OH
231
D2O
110
100
90
80
70
60
50
40
30
20
10
ppm


JAG 161
ppm
Cl
NH3
OH
HO
OH
OH
231
COSY
D2O
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 ppm


JAG 161
ppm
Cl
NH3
OH
HO
OH
OH
231
HMQC
D2O
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 ppm


JAG 169
4.25
4.25
4.24
4.23
3.91
3.87
3.78
3.74
3.60
3.59
3.56
3.55
4.04
3.99
OH
HO
OH
OH
H3N
OH
OH
Cl
232
D2O
4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 ppm
1.00
2.70
0.99
1.02
0.92

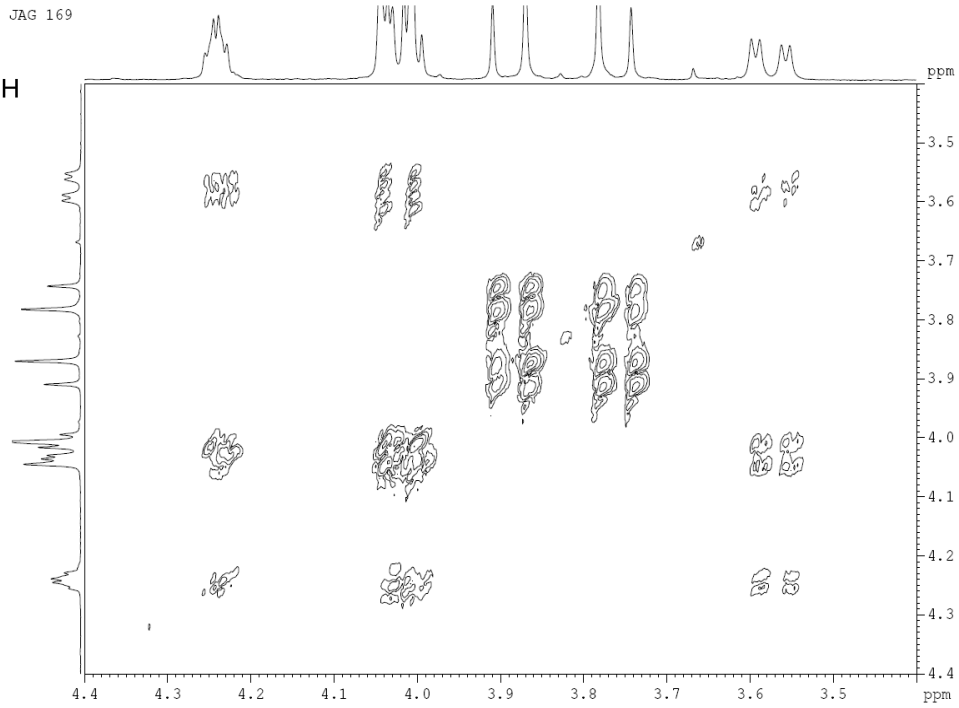

JAG 169
75.50
72.69
70.42
65.62
65.18
62.83
53.31
OH
HO
OH
OH
H3N
OH
OH
Cl
232
D2O
130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

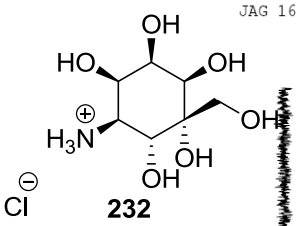


232

COSY

D_2O

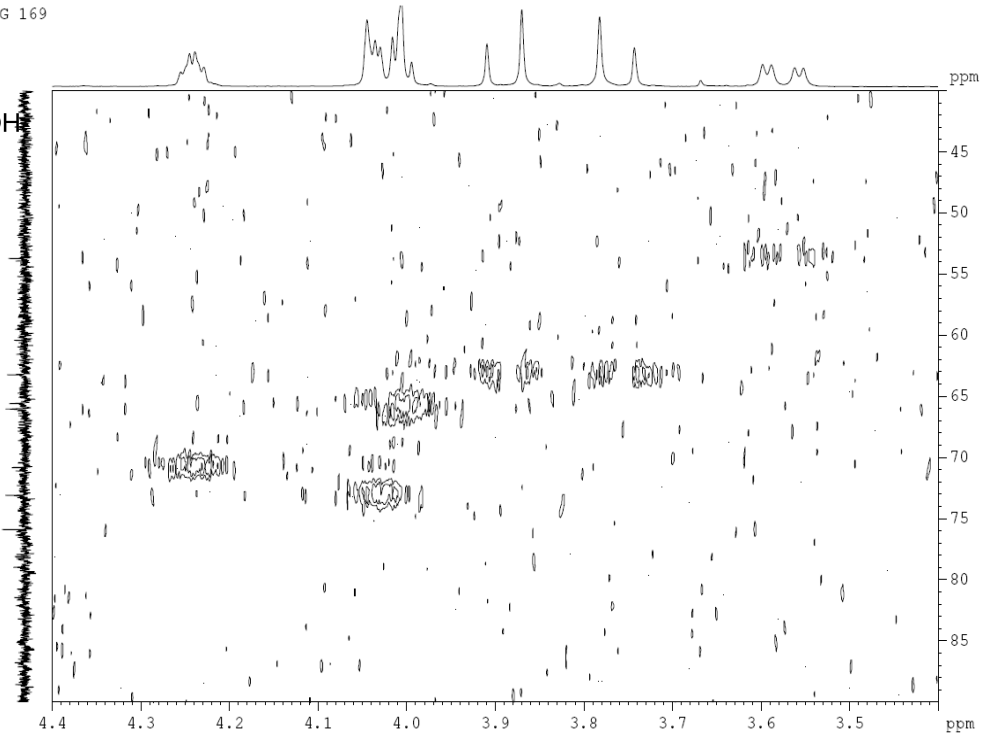


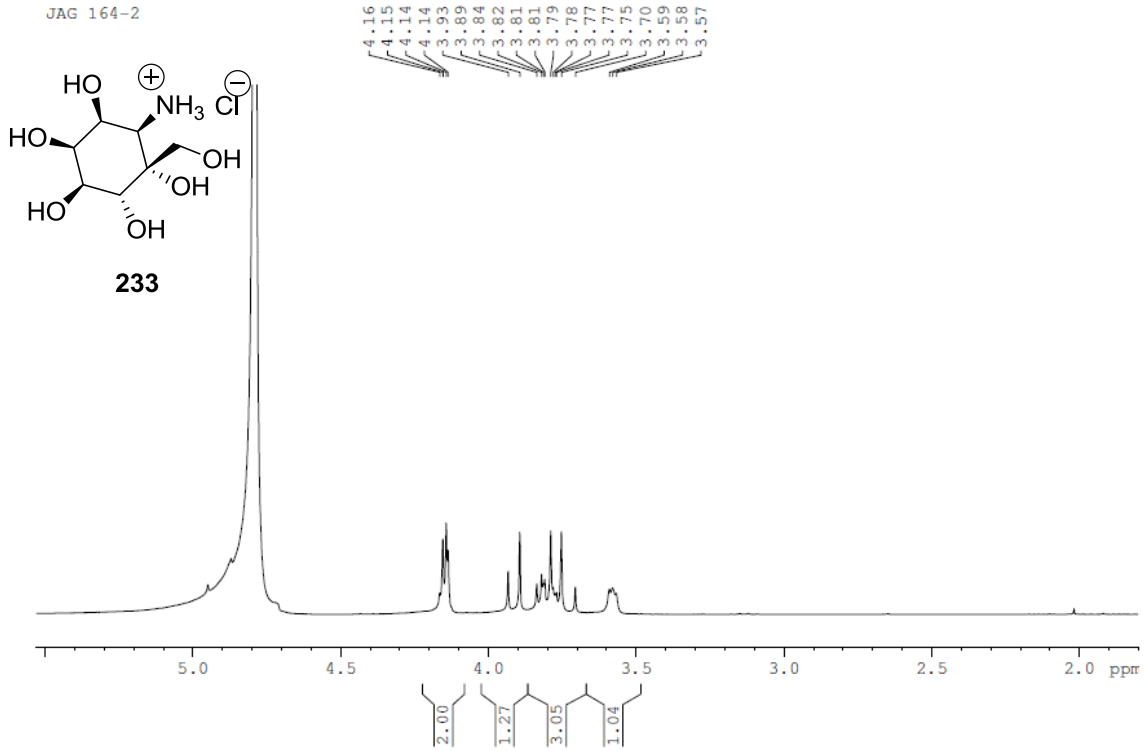


232

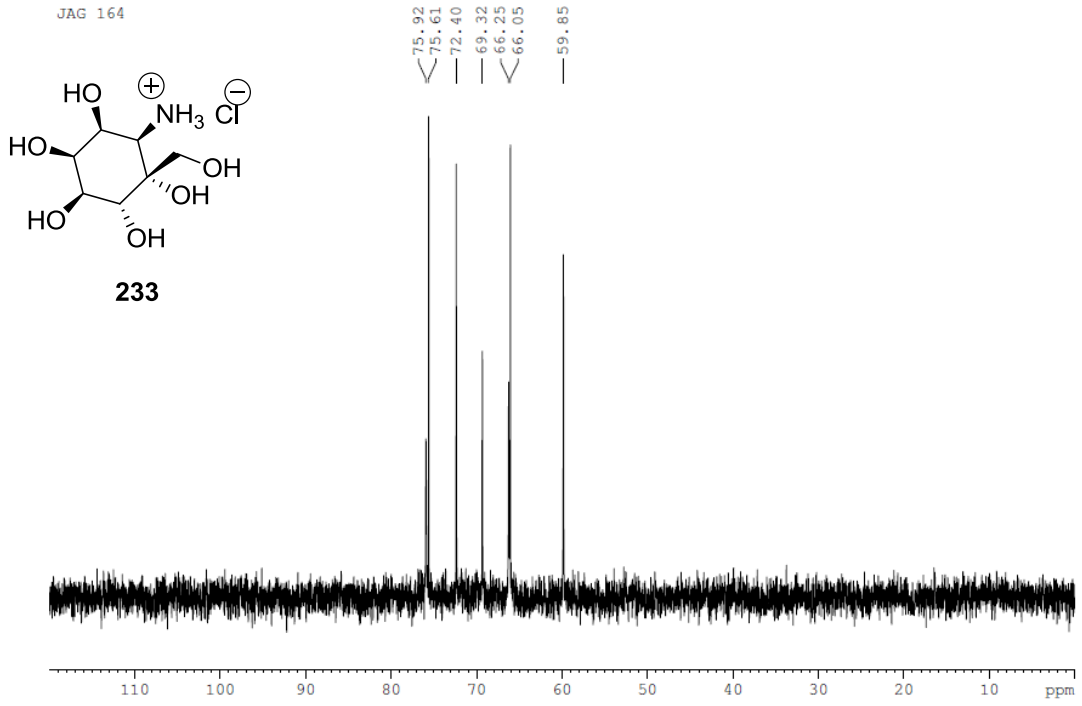
HMQC

D_2O

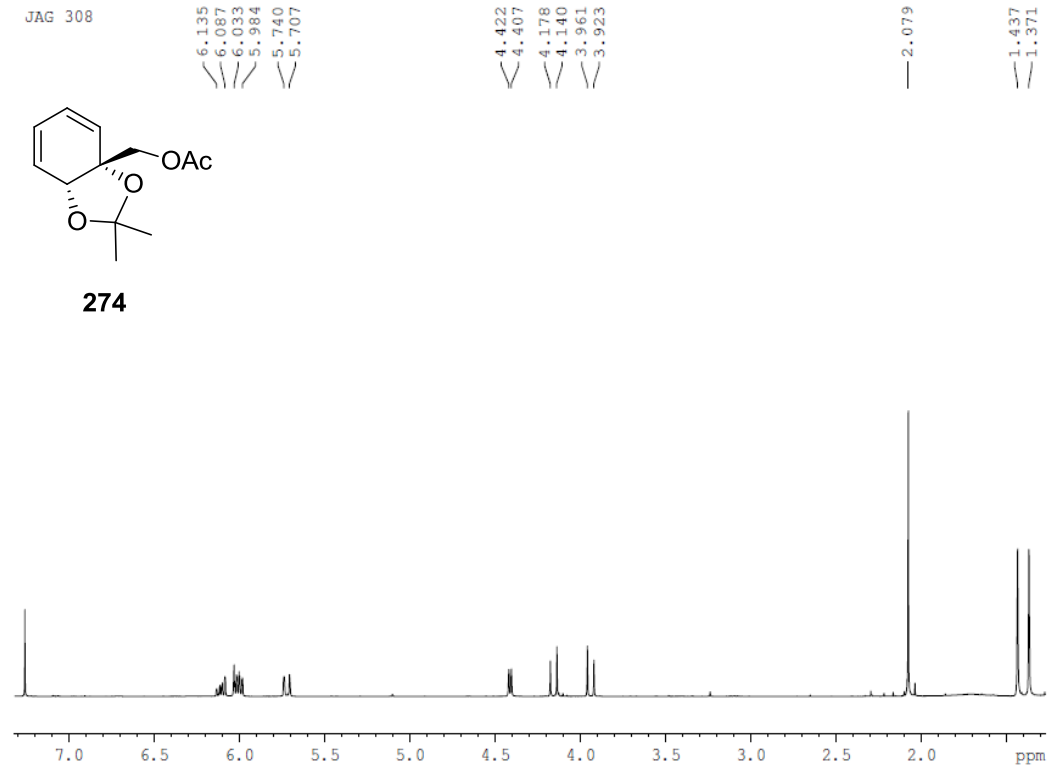



JAG 164-2
4.16
4.15
4.14
4.14
3.93
3.89
3.84
3.82
3.81
3.81
3.79
3.78
3.77
3.77
3.75
3.70
3.59
3.58
3.57
HO
NH3 Cl
HO
OH
OH
HO
OH
5.0
4.5
4.0
3.5
3.0
2.5
2.0 ppm
2.00
1.27
3.05
1.04

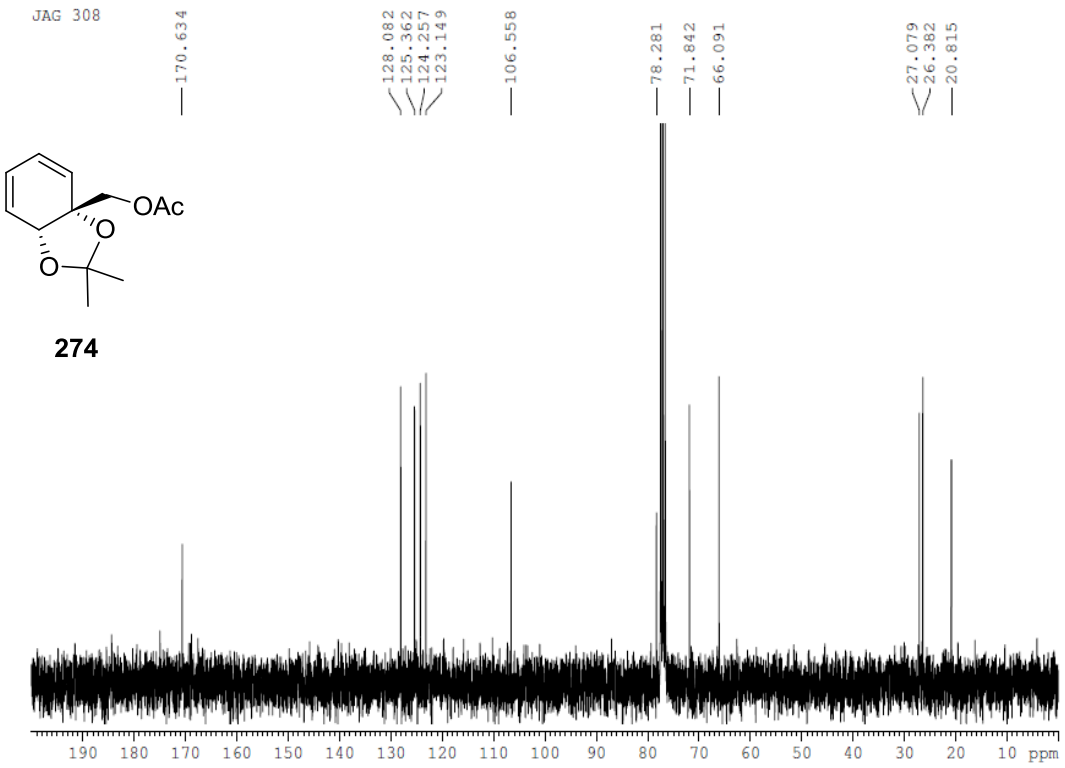
233


JAG 164
75.92
75.61
72.40
69.32
66.25
66.05
59.85
HO
NH3 Cl
HO
OH
OH
HO
OH
110
100
90
80
70
60
50
40
30
20
10
ppm

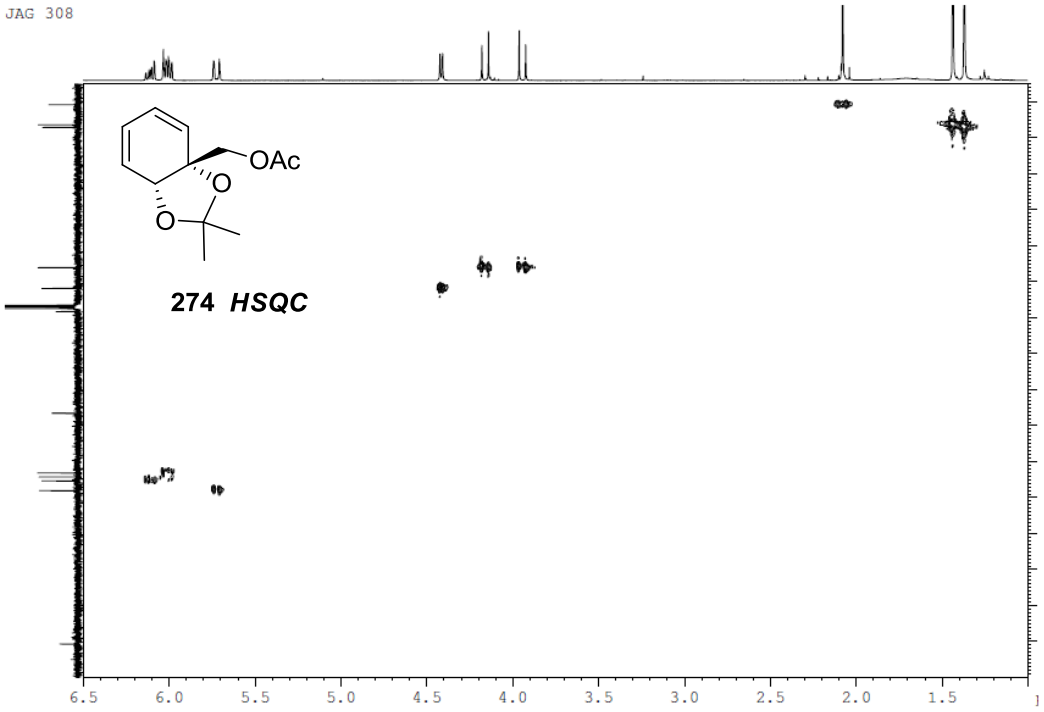
233

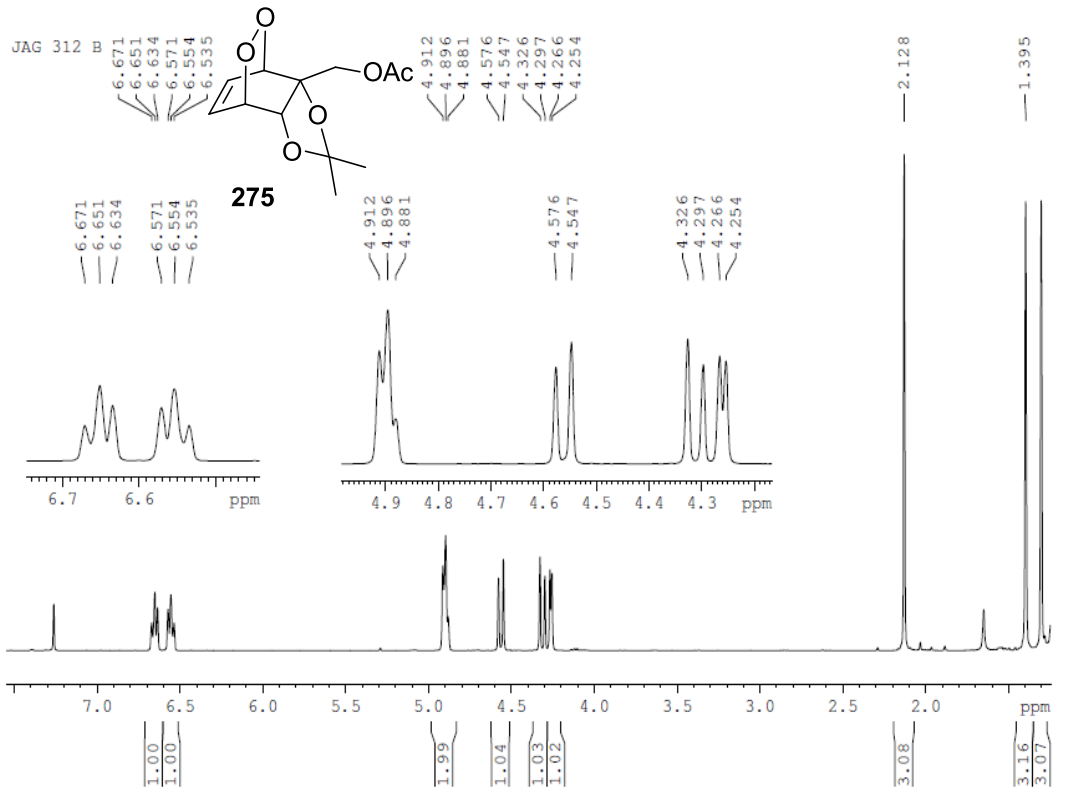

JAG 308
6.135
6.087
6.033
5.984
5.740
5.707
4.422
4.407
4.178
4.140
3.961
3.923
2.079
1.437
1.371
OAc
O
O
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

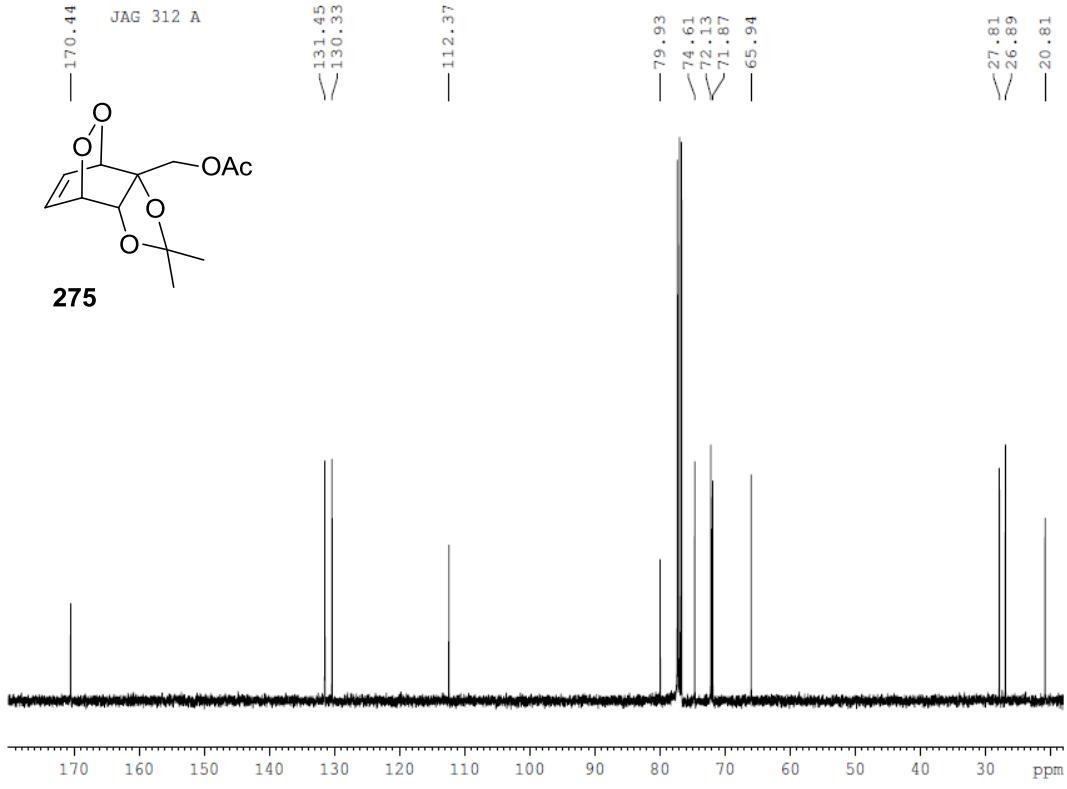
274

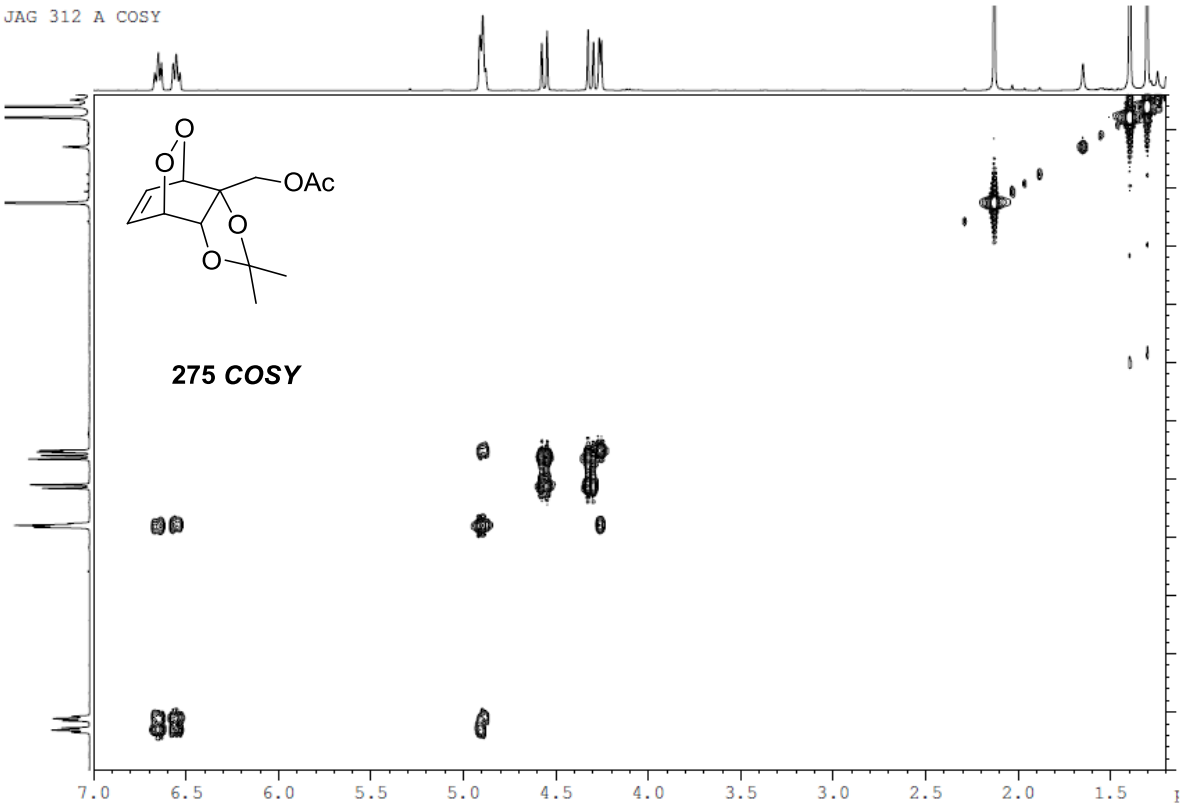

JAG 308
170.634
128.082
125.362
124.257
123.149
106.558
78.281
71.842
66.091
27.079
26.382
20.815
OAc
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

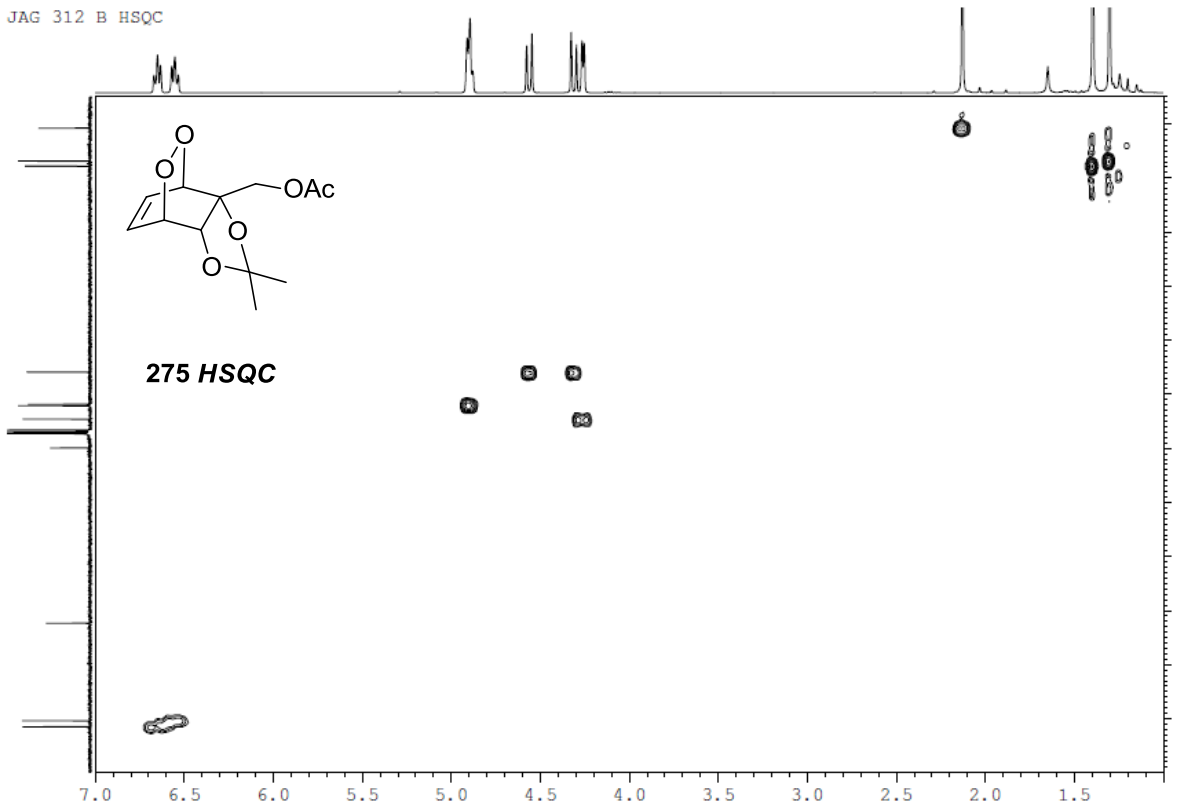
274

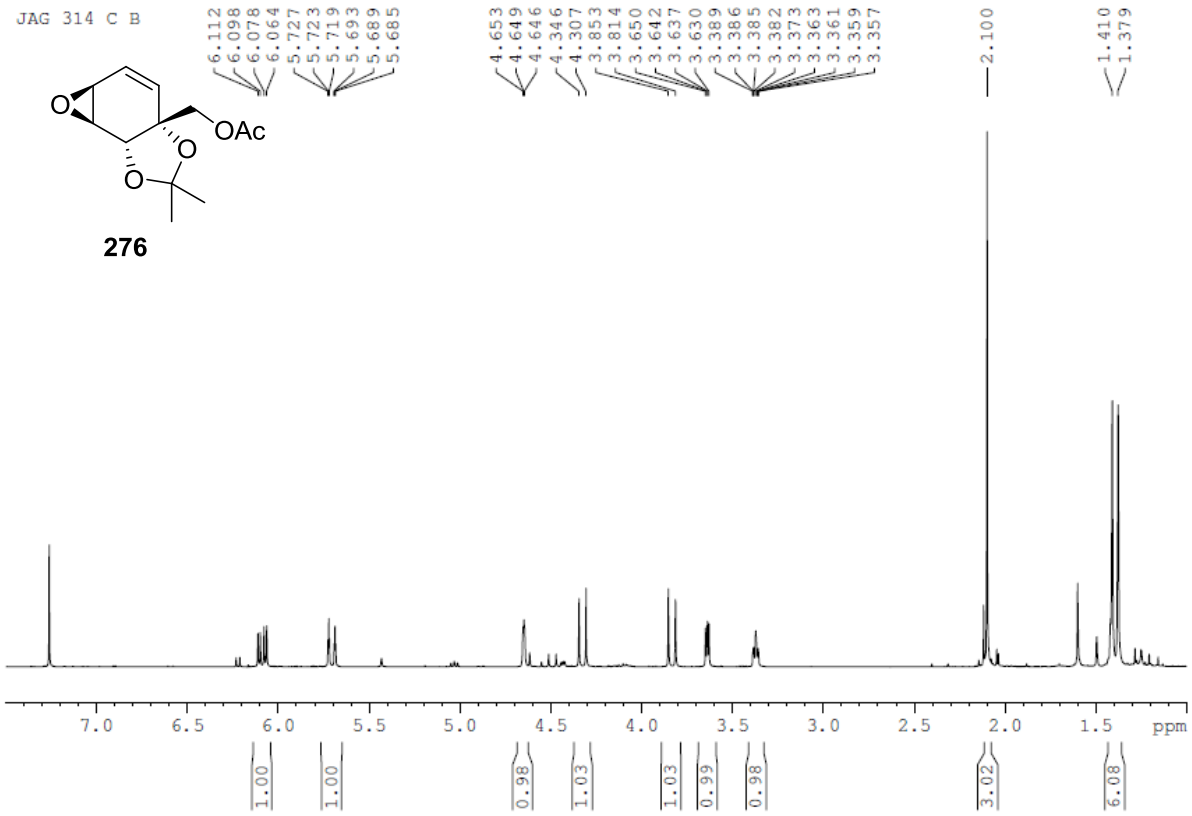

JAG 308
OAc
O
O
274 HSQC
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

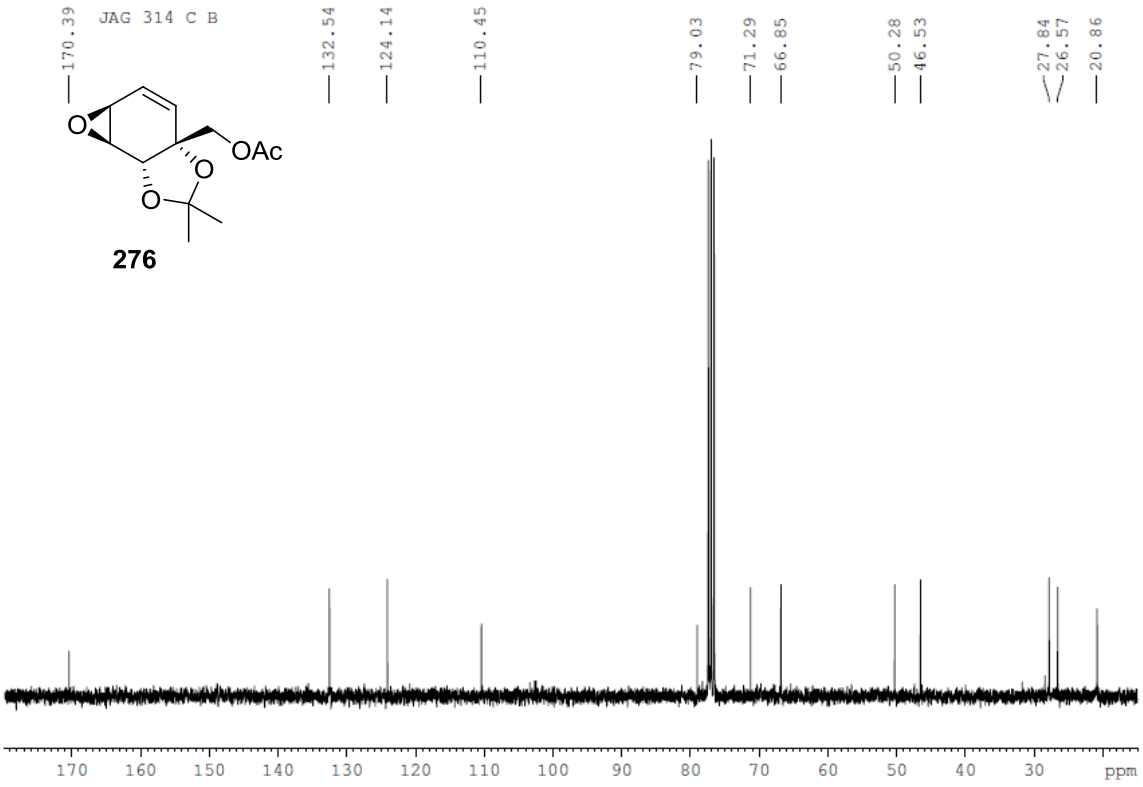

JAG 312 B
6.671
6.651
6.634
6.571
6.554
6.535
4.912
4.896
4.881
4.576
4.547
4.326
4.297
4.266
4.254
2.128
1.395
OAc
O
O
O
275
ppm
1.00
1.00
1.99
1.04
1.03
1.02
3.08
3.16
3.07

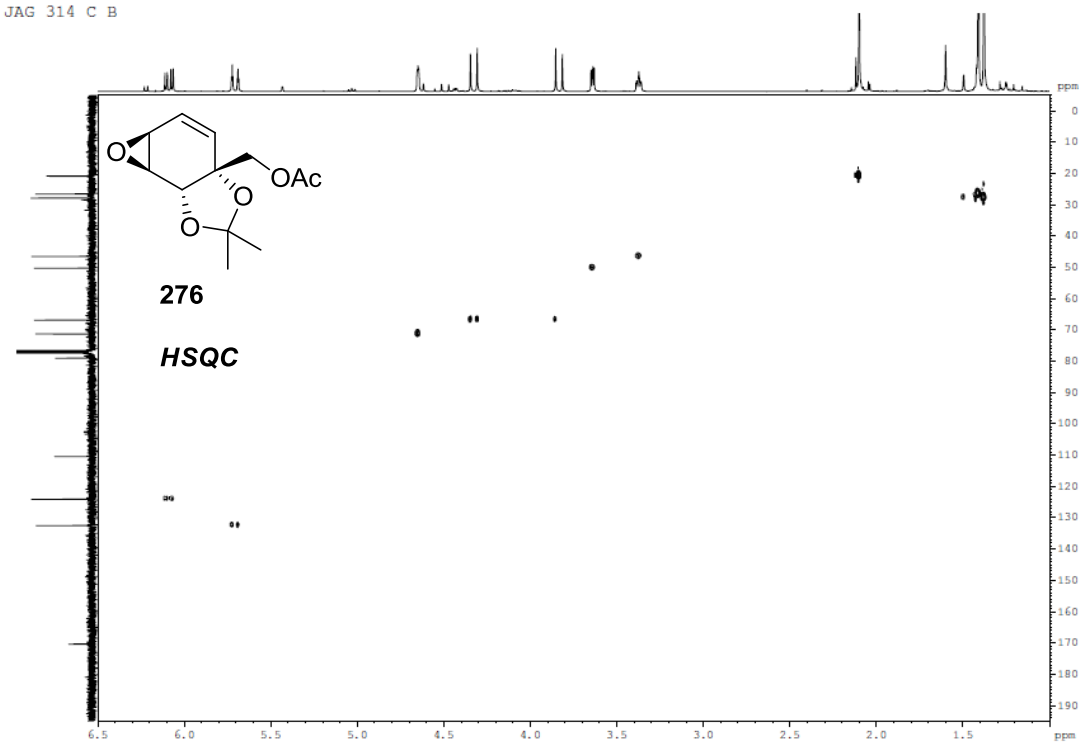

JAG 312 A
170.44
131.45
130.33
112.37
79.93
74.61
72.13
71.87
65.94
27.81
26.89
20.81
OAc
O
O
O
275
ppm

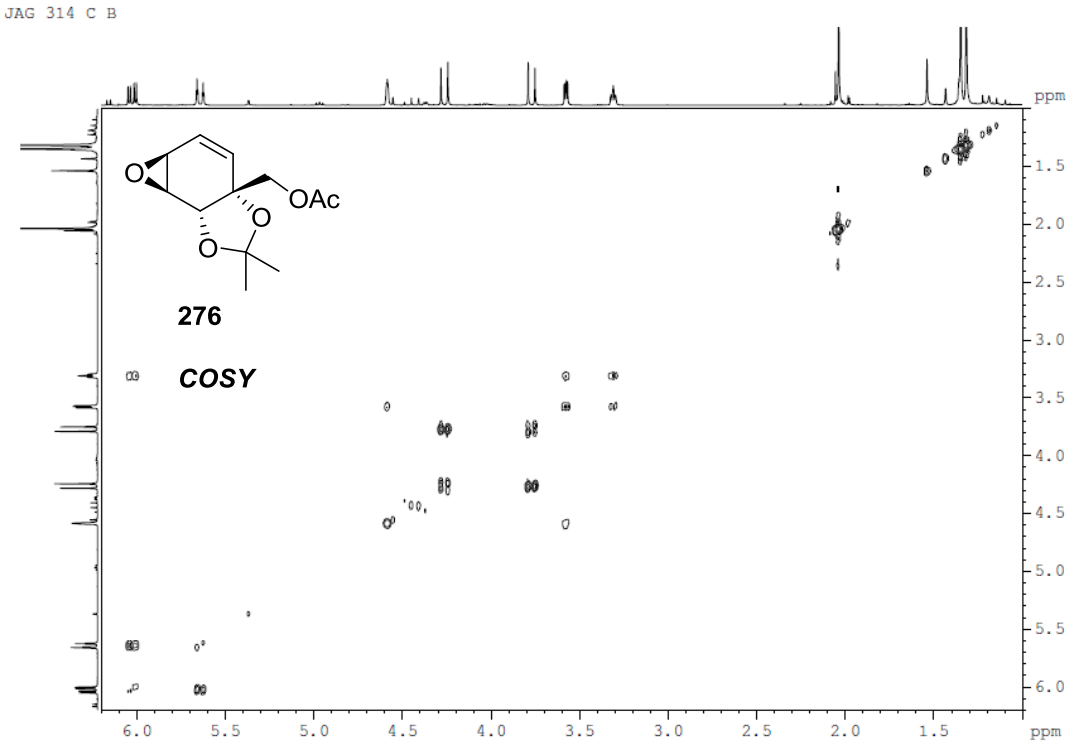

JAG 312 A COSY
O
O
OAc
O
O
275 COSY
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

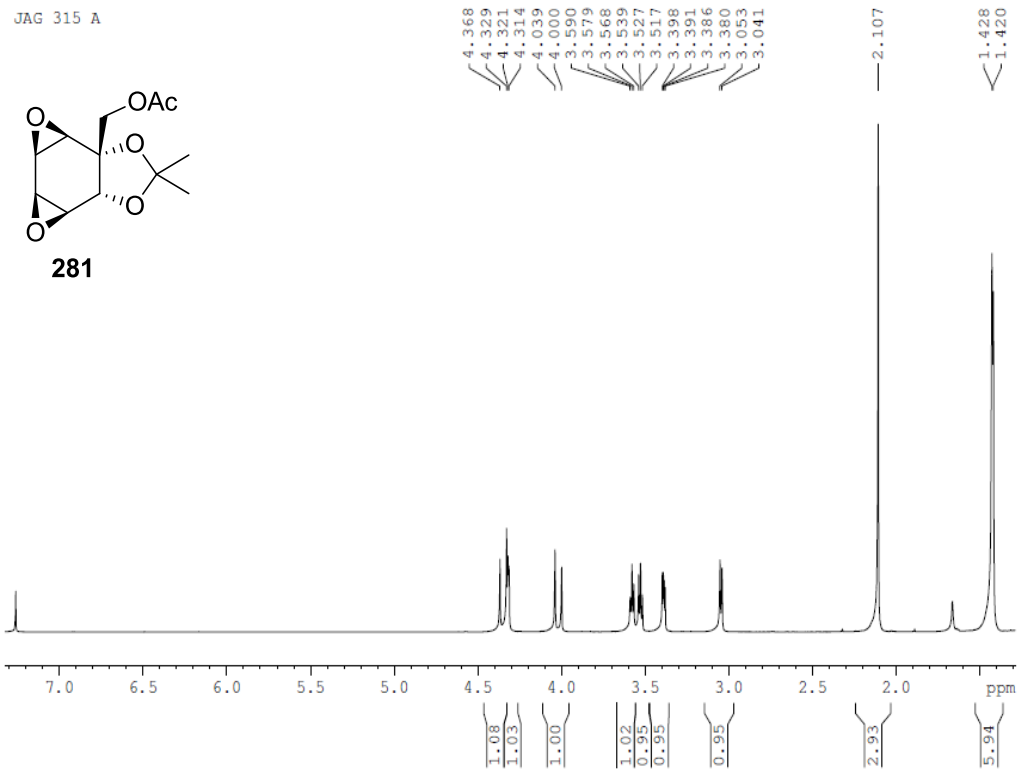

JAG 312 B HSQC
O
O
OAc
O
O
275 HSQC
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

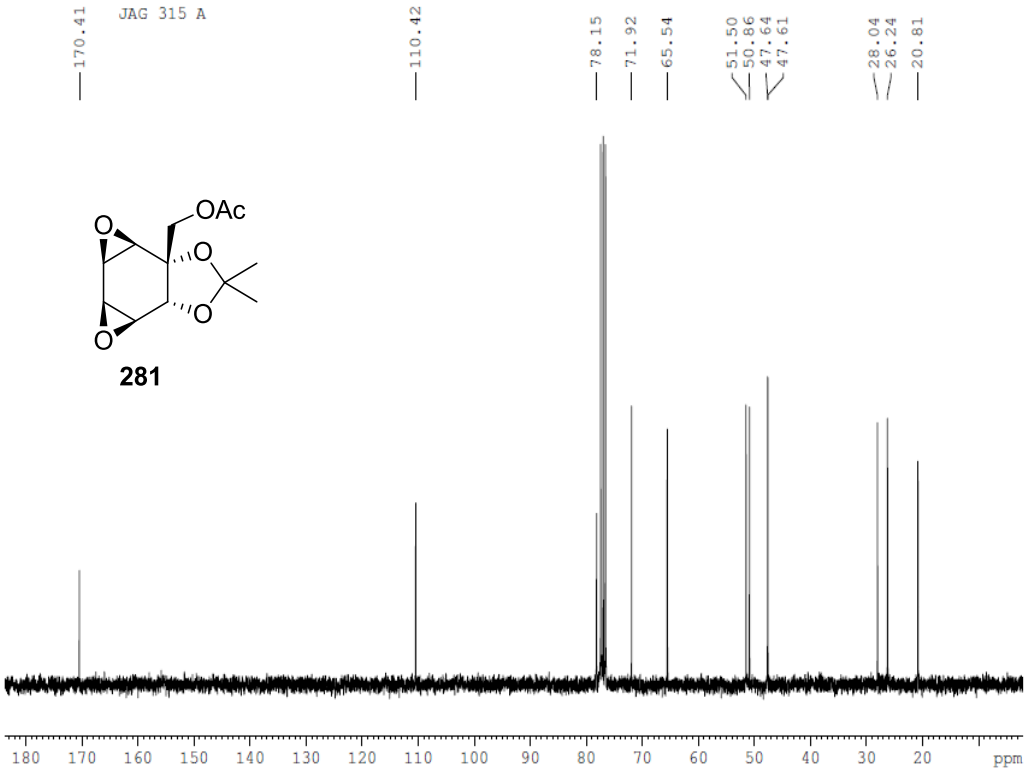

JAG 314 C B
6.112
6.098
6.078
6.064
5.727
5.723
5.719
5.693
5.689
5.685
4.653
4.649
4.646
4.346
4.307
3.853
3.814
3.650
3.642
3.637
3.630
3.389
3.386
3.385
3.382
3.373
3.363
3.361
3.359
3.357
2.100
1.410
1.379
OAc
O
O
O
276
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.00
0.98
1.03
1.03
0.99
0.98
3.02
6.08

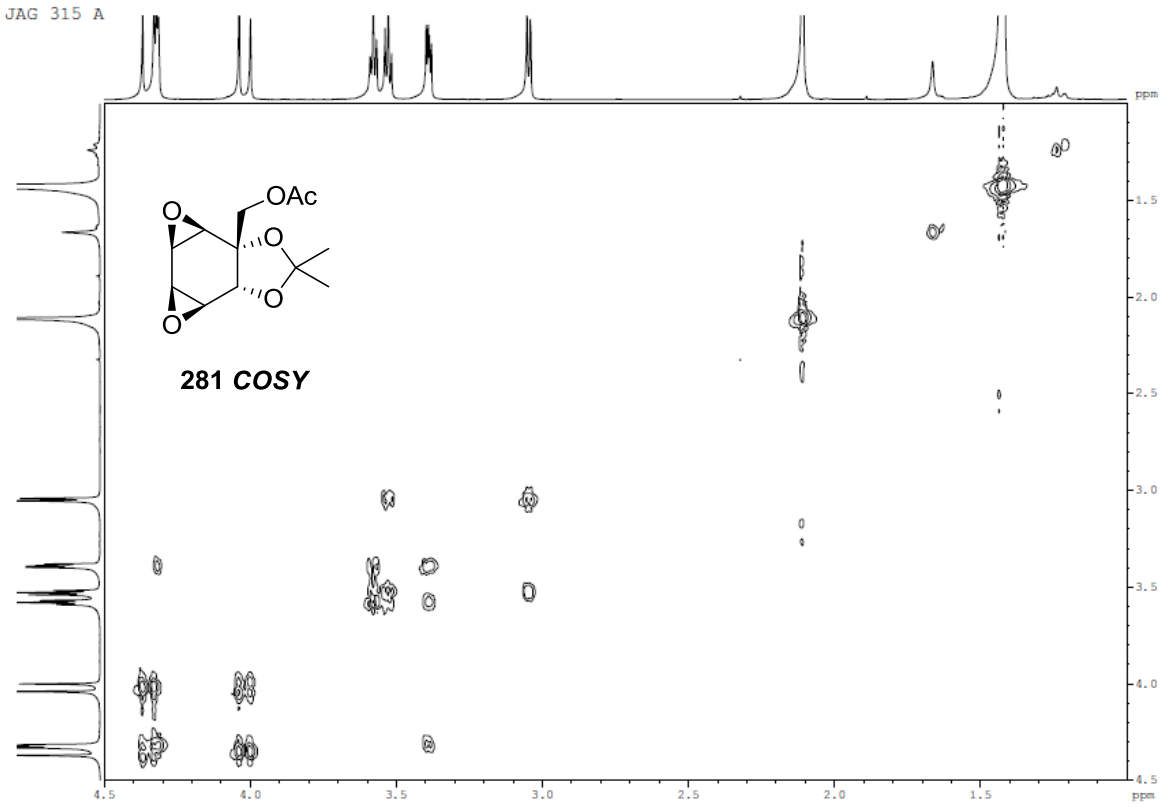

JAG 314 C B
170.39
132.54
124.14
110.45
79.03
71.29
66.85
50.28
46.53
27.84
26.57
20.86
OAc
O
O
O
276
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

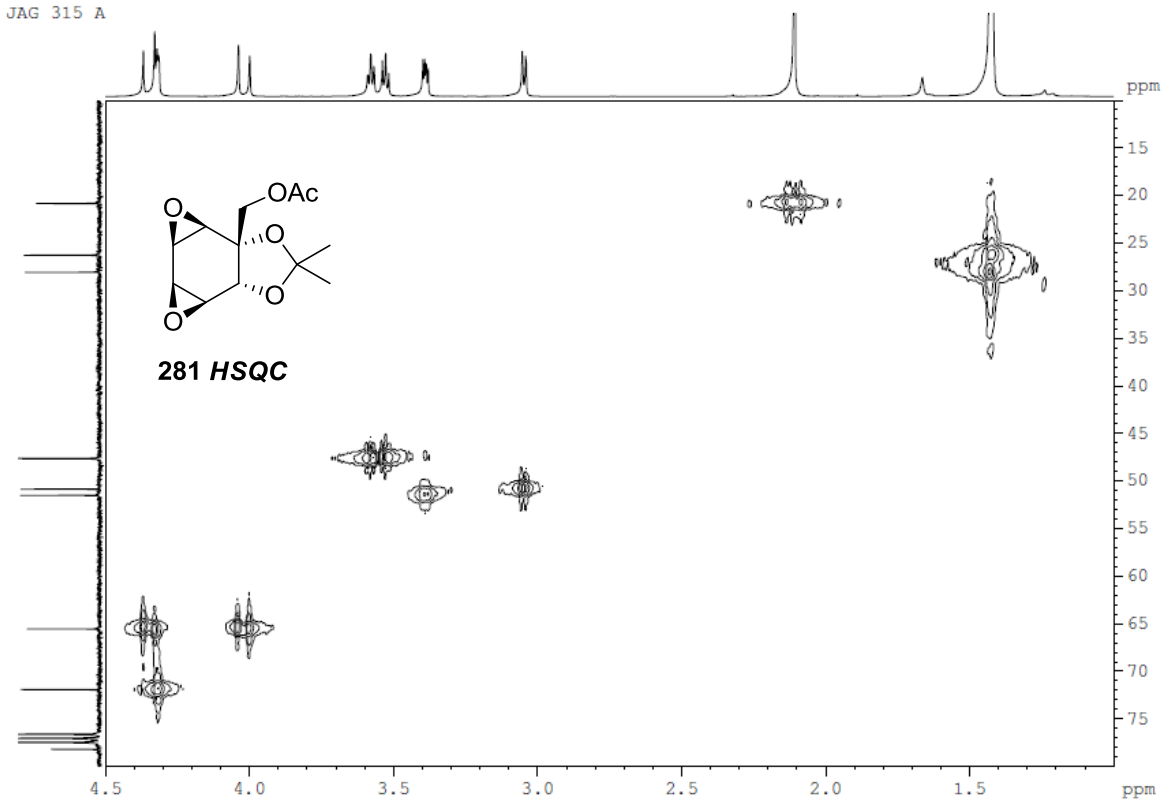

JAG 314 C B
OAc
276
HSQC
ppm
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

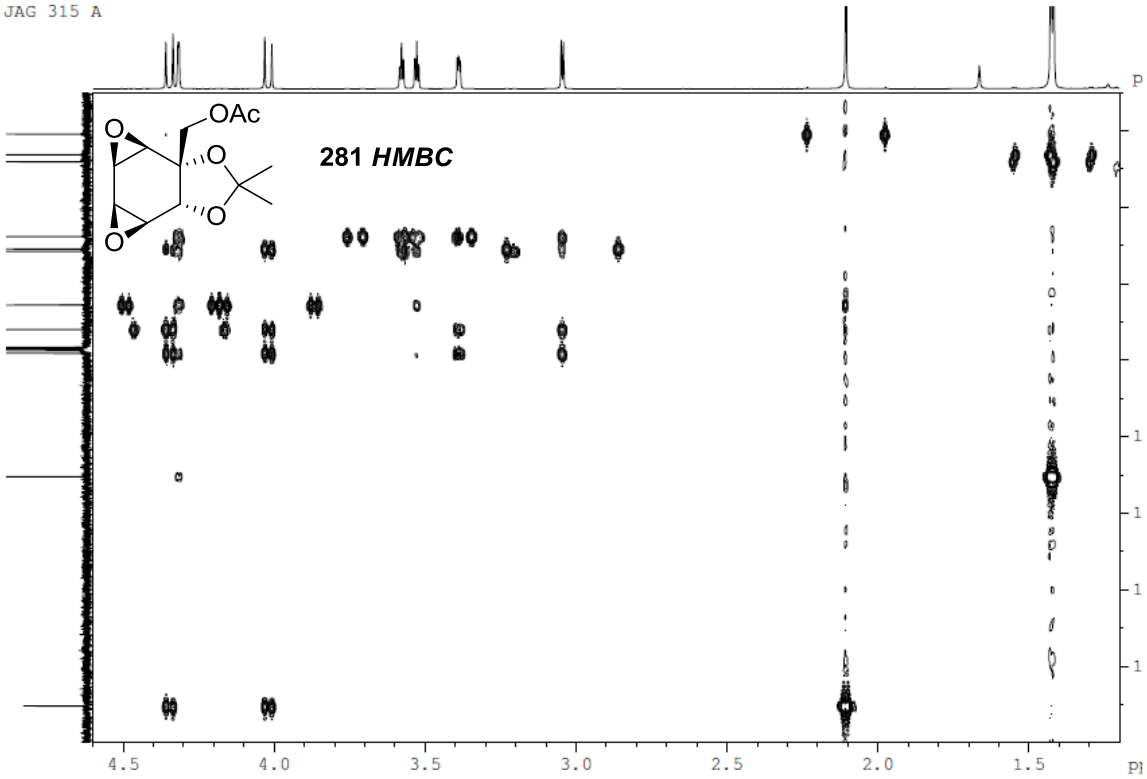

JAG 314 C B
OAc
276
COSY
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

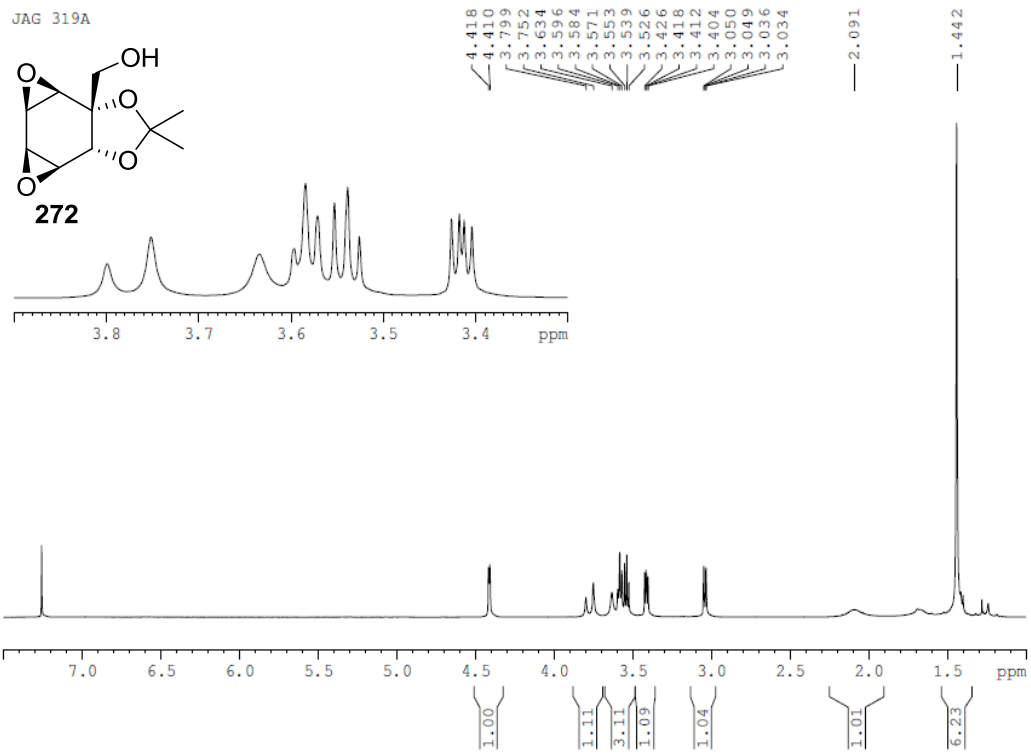

JAG 315 A
OAc
O
O
O
281
4.368
4.329
4.321
4.314
4.039
4.000
3.590
3.579
3.568
3.539
3.527
3.517
3.398
3.391
3.386
3.380
3.053
3.041
2.107
1.428
1.420
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.08
1.03
1.00
1.02
0.95
0.95
0.95
2.93
5.94

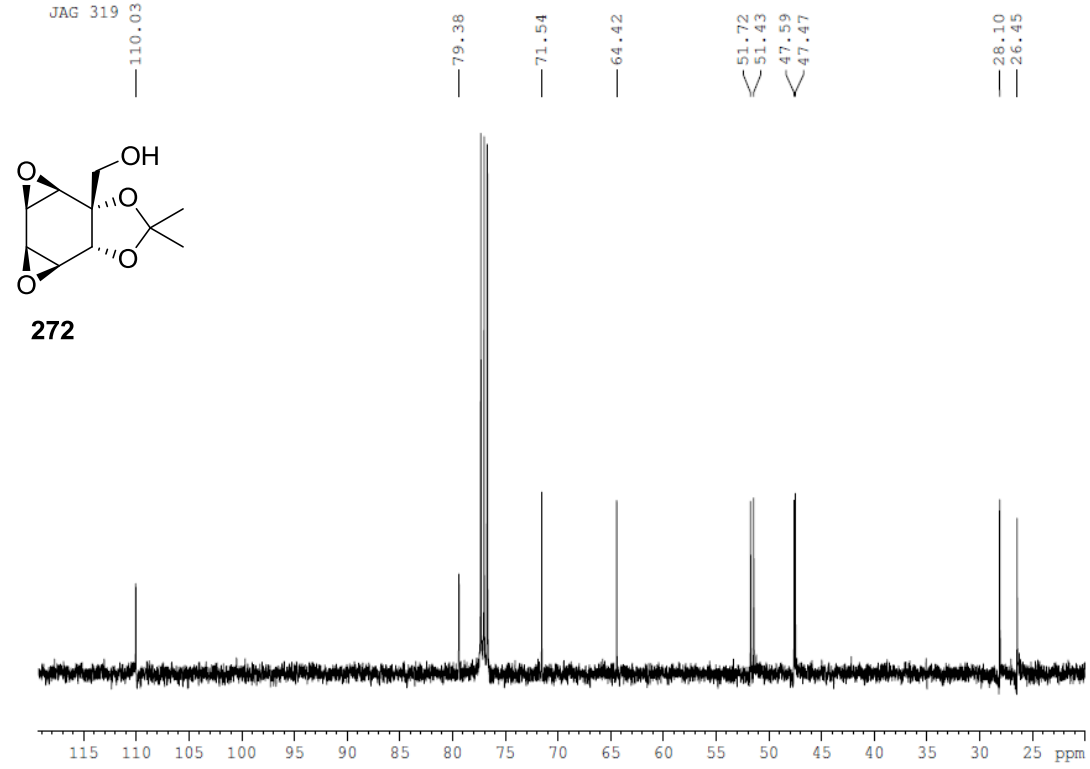

JAG 315 A
170.41
110.42
78.15
71.92
65.54
51.50
50.86
47.64
47.61
28.04
26.24
20.81
OAc
O
O
O
281
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

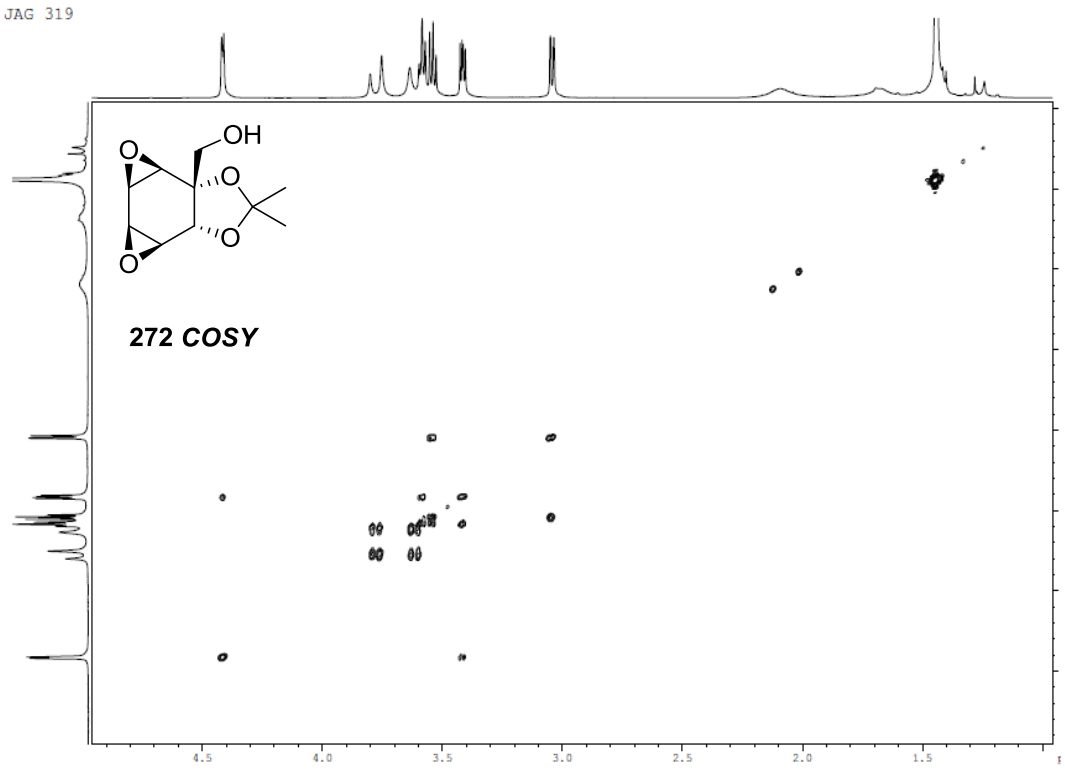

JAG 315 A
OAc
O
O
O
O
281 COSY
ppm
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

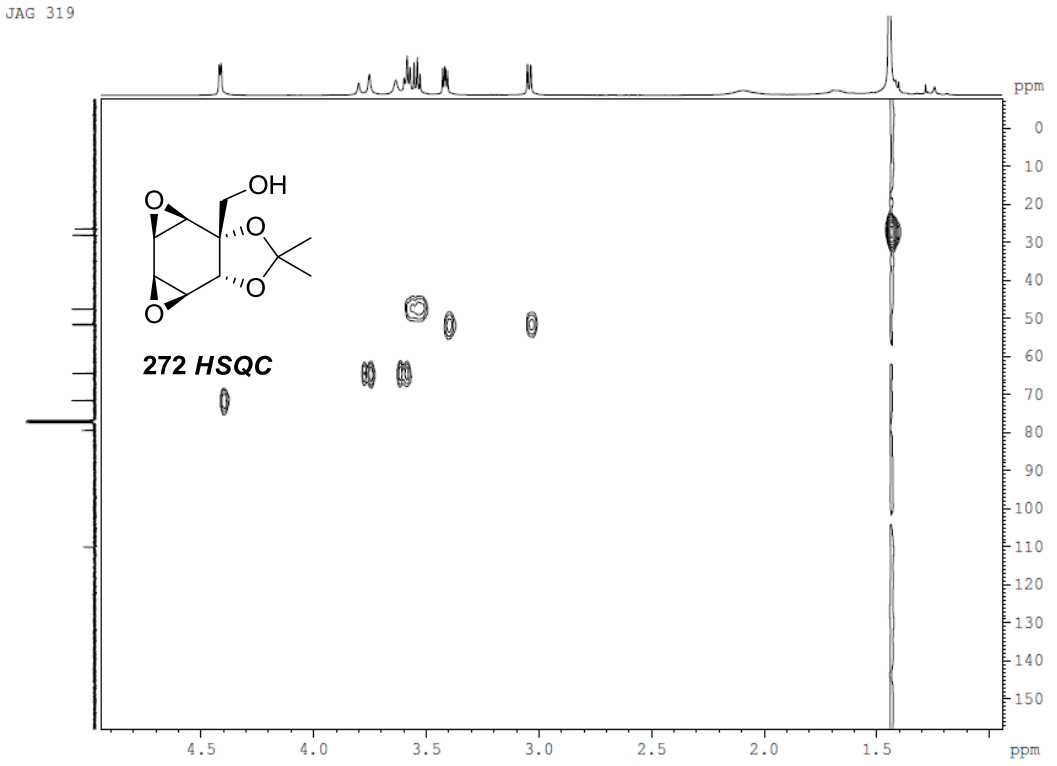

JAG 315 A
OAc
O
O
O
O
281 HSQC
ppm
15
20
25
30
35
40
45
50
55
60
65
70
75
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

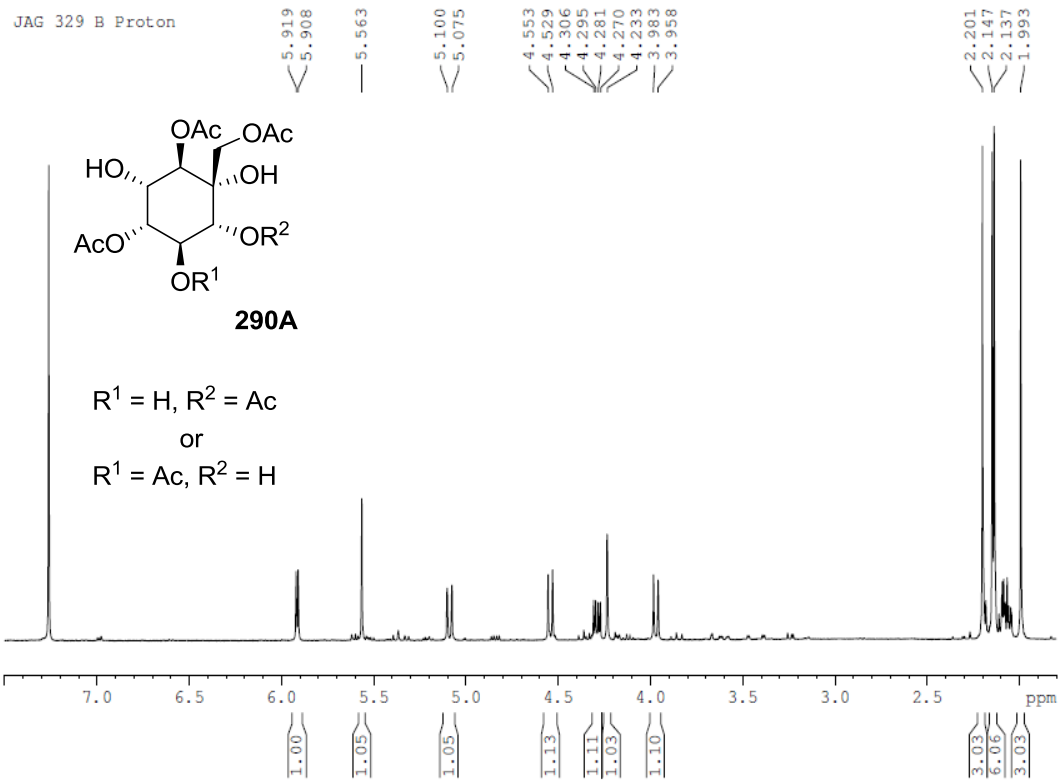

JAG 315 A
OAc
O
O
O
O
281 HMBC
4.5
4.0
3.5
3.0
2.5
2.0
1.5

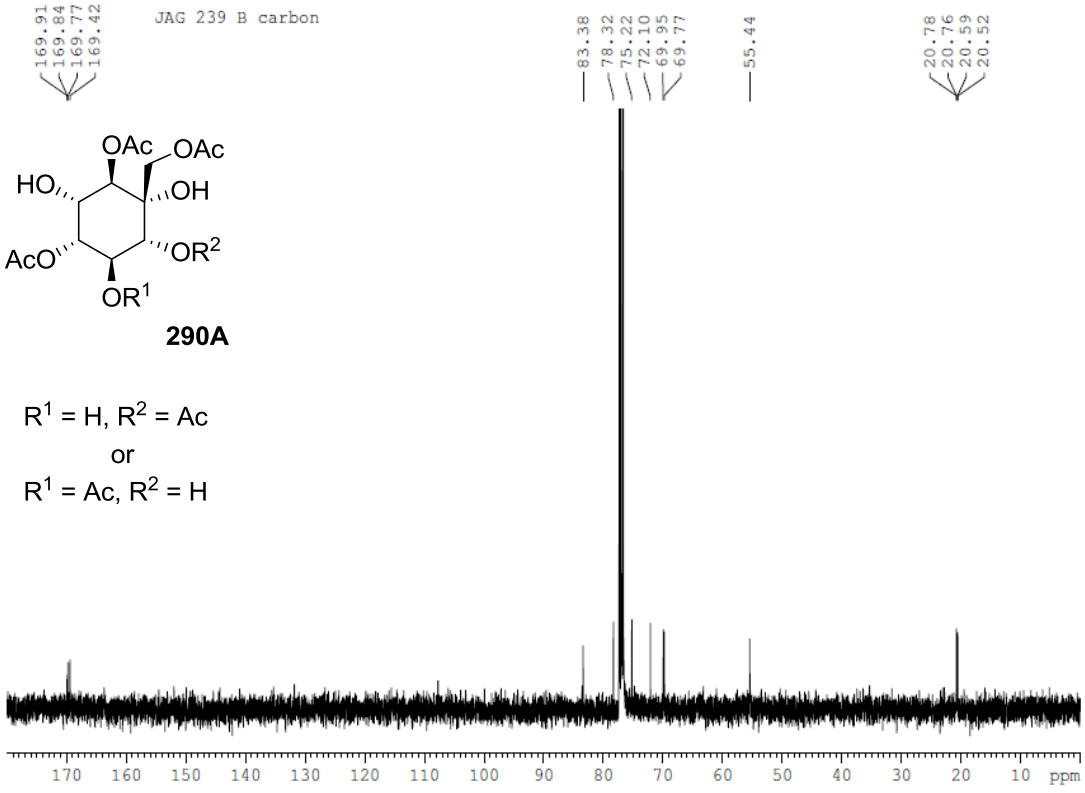

JAG 319A
OH
O
O
O
O
272
4.418
4.410
3.799
3.752
3.634
3.596
3.584
3.571
3.553
3.539
3.526
3.426
3.418
3.412
3.404
3.050
3.049
3.036
3.034
2.091
1.442
3.8
3.7
3.6
3.5
3.4
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.11
3.11
1.09
1.04
1.01
6.23

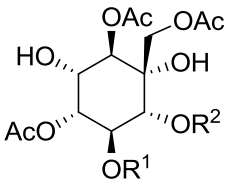

JAG 319
110.03
79.38
71.54
64.42
51.72
51.43
47.59
47.47
28.10
26.45
OH
O
O
O
O
272
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
ppm


JAG 319
OH
O
O
O
O
272 COSY
4.5
4.0
3.5
3.0
2.5
2.0
1.5


JAG 319
OH
O
O
O
O
272 HSQC
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

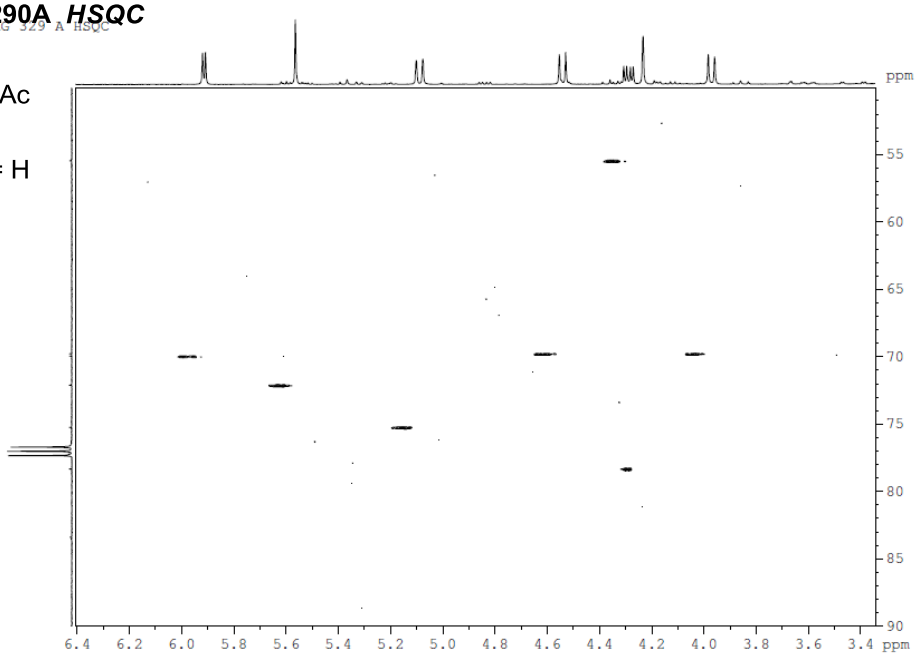

JAG 329 B Proton
5.919
5.908
5.563
5.100
5.075
4.553
4.529
4.306
4.295
4.281
4.270
4.233
3.983
3.958
2.201
2.147
2.137
1.993
OAc
OAc
HO
OH
AcO
OR2
OR1
290A
R1 = H, R2 = Ac
or
R1 = Ac, R2 = H
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
1.00
1.05
1.05
1.13
1.11
1.03
1.10
3.03
6.06
3.03

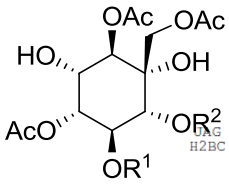

169.91
169.84
169.77
169.42
JAG 239 B carbon
83.38
78.32
75.22
72.10
69.95
69.77
55.44
20.78
20.76
20.59
20.52
OAc
OAc
HO
OH
AcO
OR2
OR1
290A
R1 = H, R2 = Ac
or
R1 = Ac, R2 = H
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



290A *HSQC*

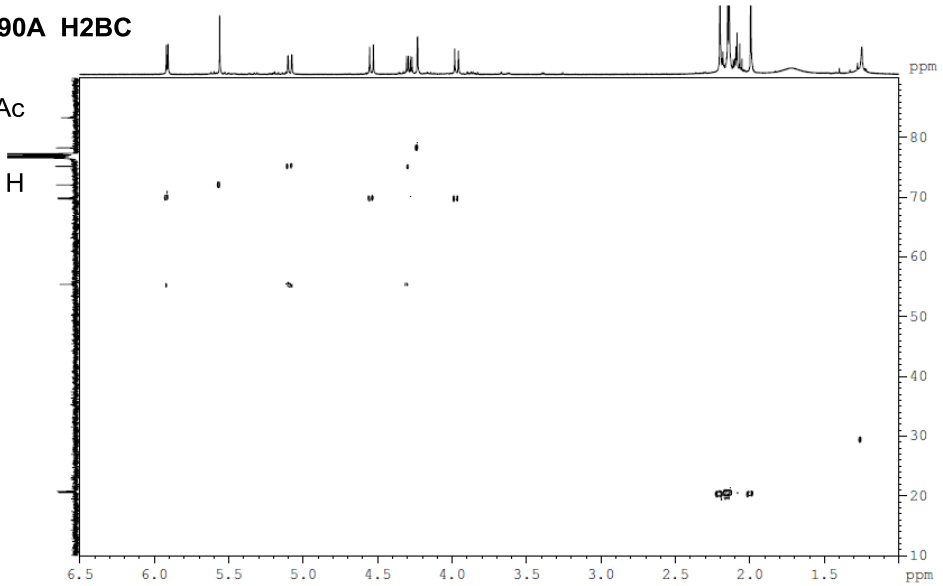
R^1 = H, R^2 = Ac
or
R^1 = Ac, R^2 = H

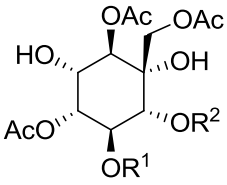




290A H2BC

R^1 = H, R^2 = Ac
or
R^1 = Ac, R^2 = H



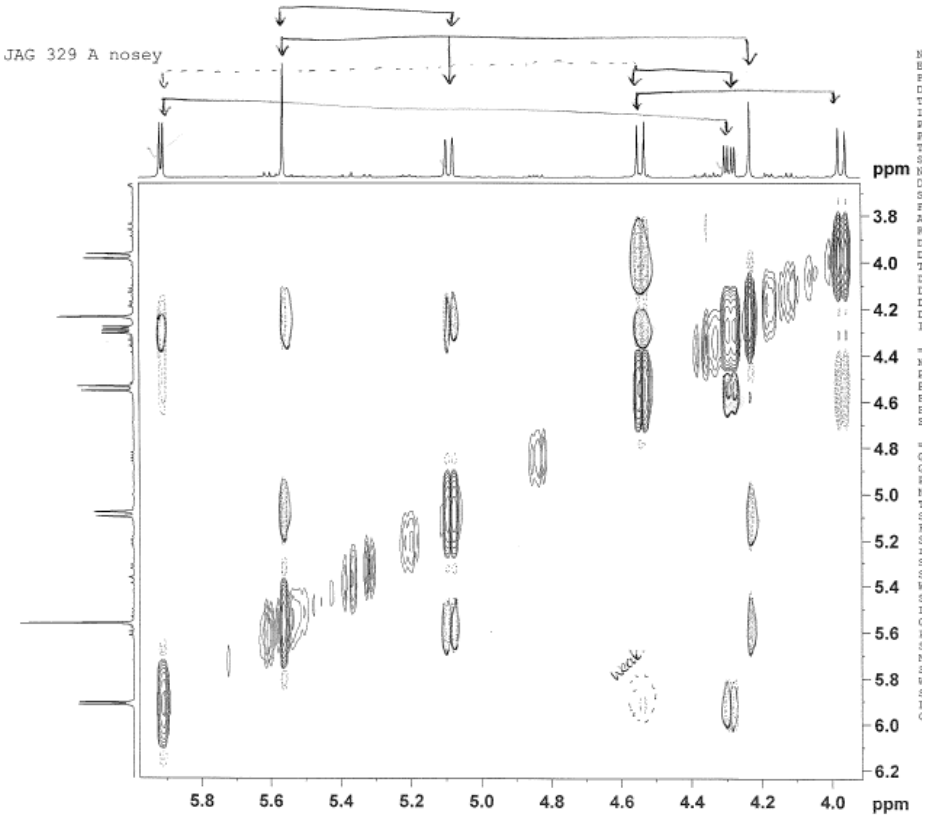


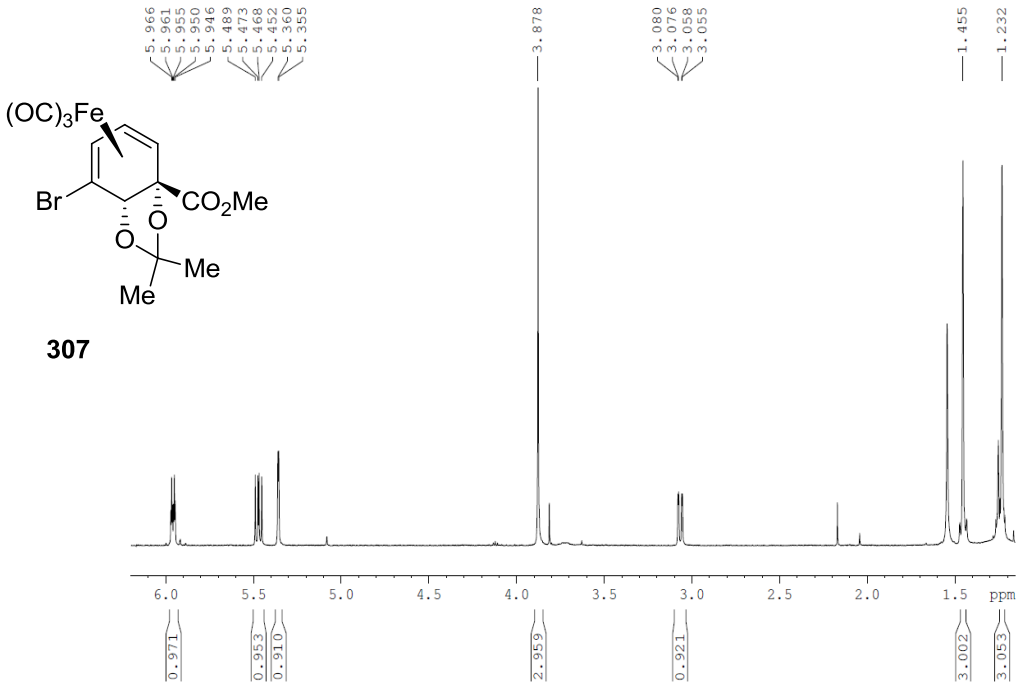
290A NOESY

R^1 = H, R^2 = Ac

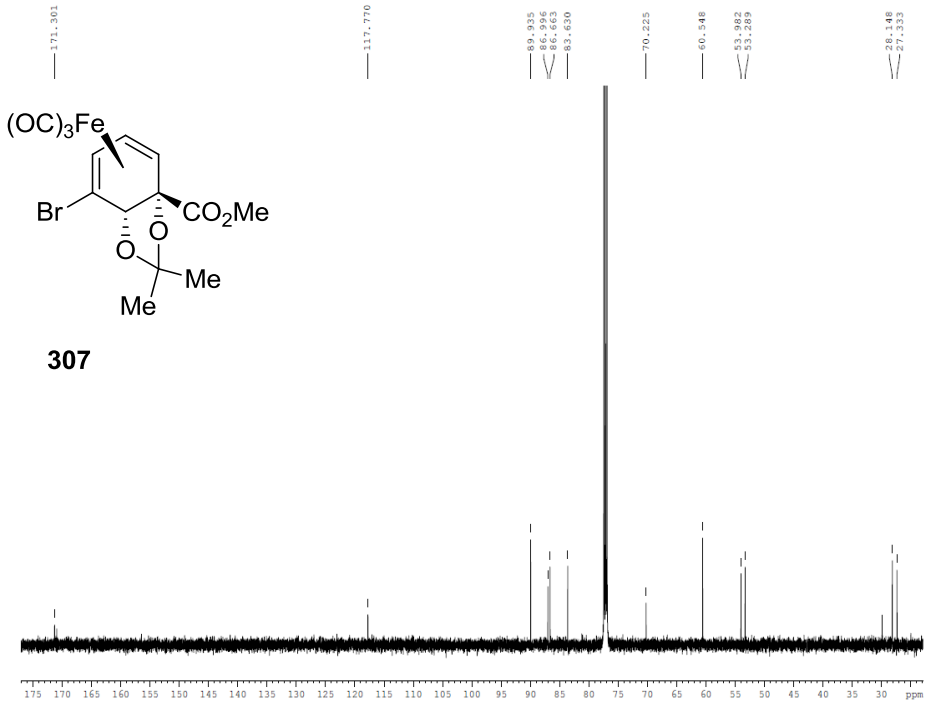
or

R^1 = Ac, R^2 = H

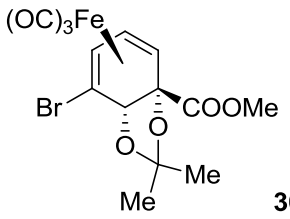



5.966
5.961
5.955
5.950
5.946
5.489
5.473
5.468
5.452
5.360
5.355
3.878
3.080
3.076
3.058
3.055
1.455
1.232
(OC)3Fe
Br
CO2Me
O
O
Me
Me
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.971
0.953
0.910
2.959
0.921
3.002
3.053

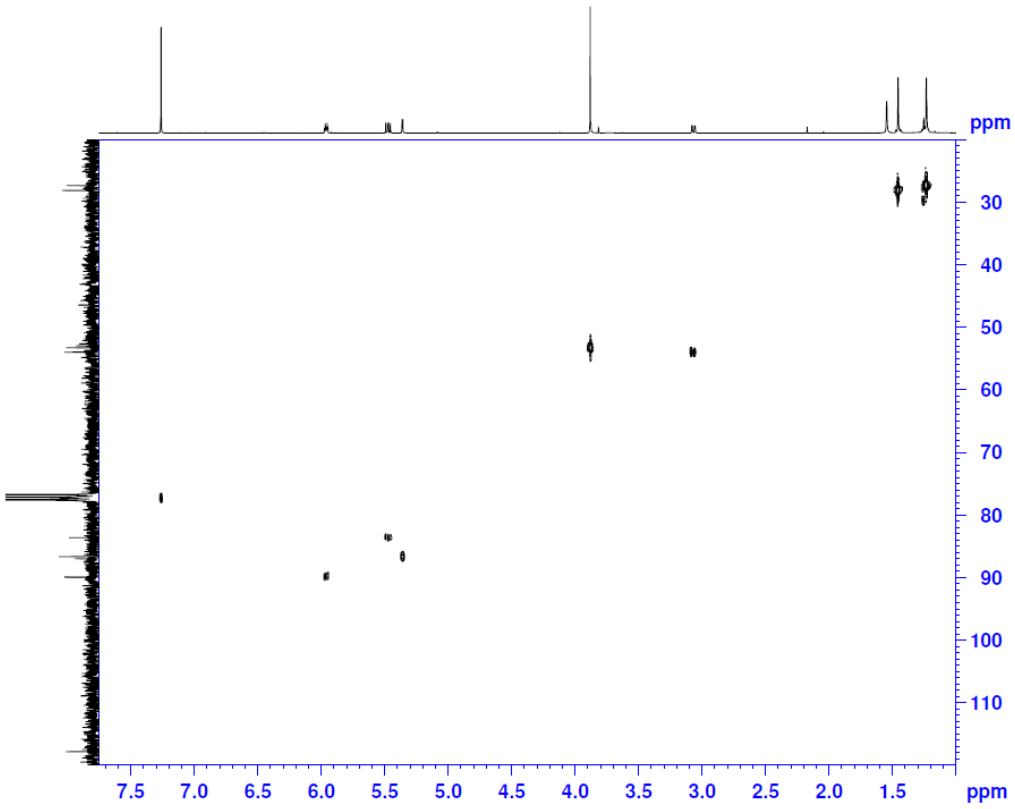
307

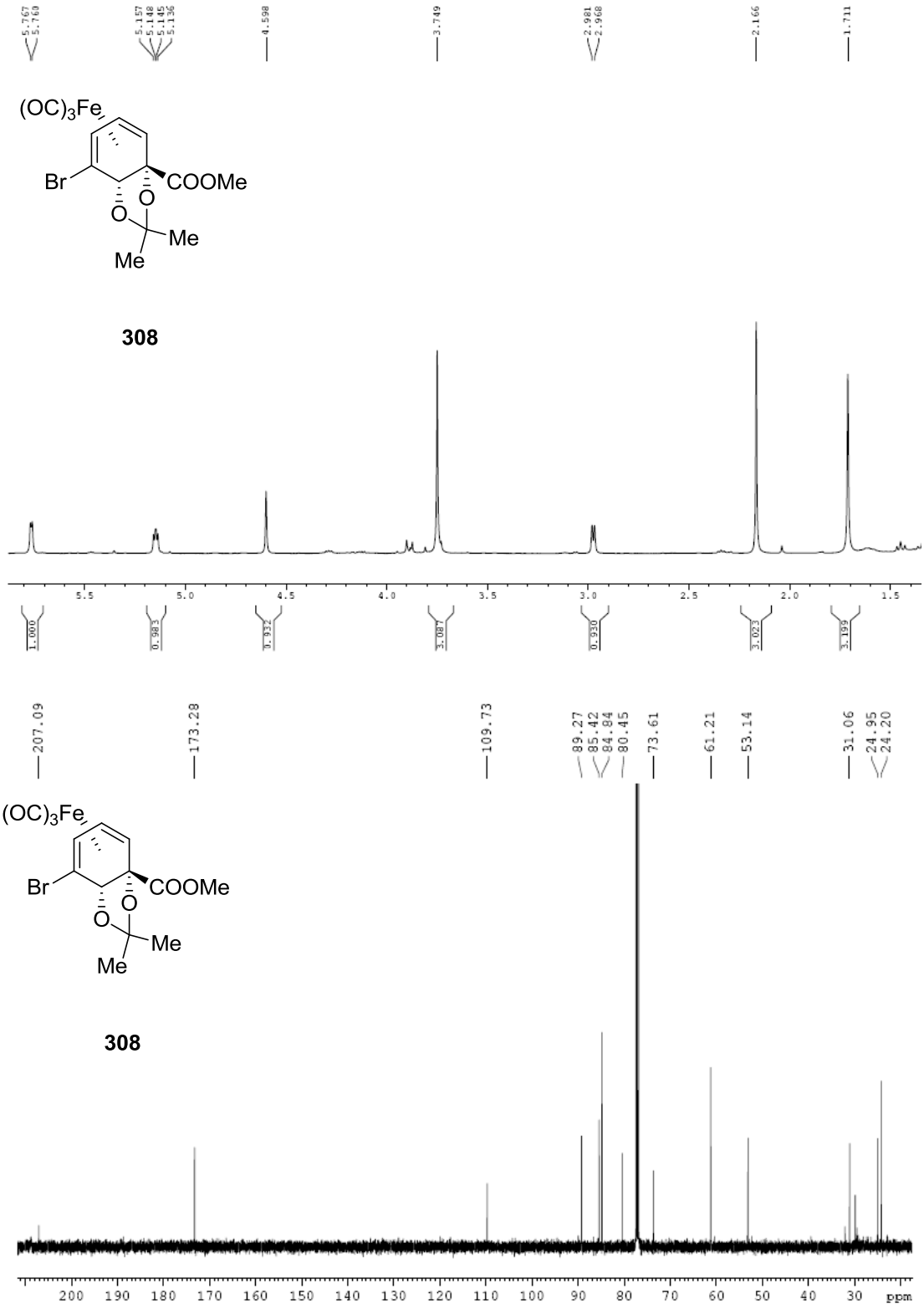

171.301
117.770
89.935
86.996
86.663
83.630
70.225
60.548
53.982
53.289
28.148
27.333
(OC)3Fe
Br
CO2Me
O
O
Me
Me
175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 ppm

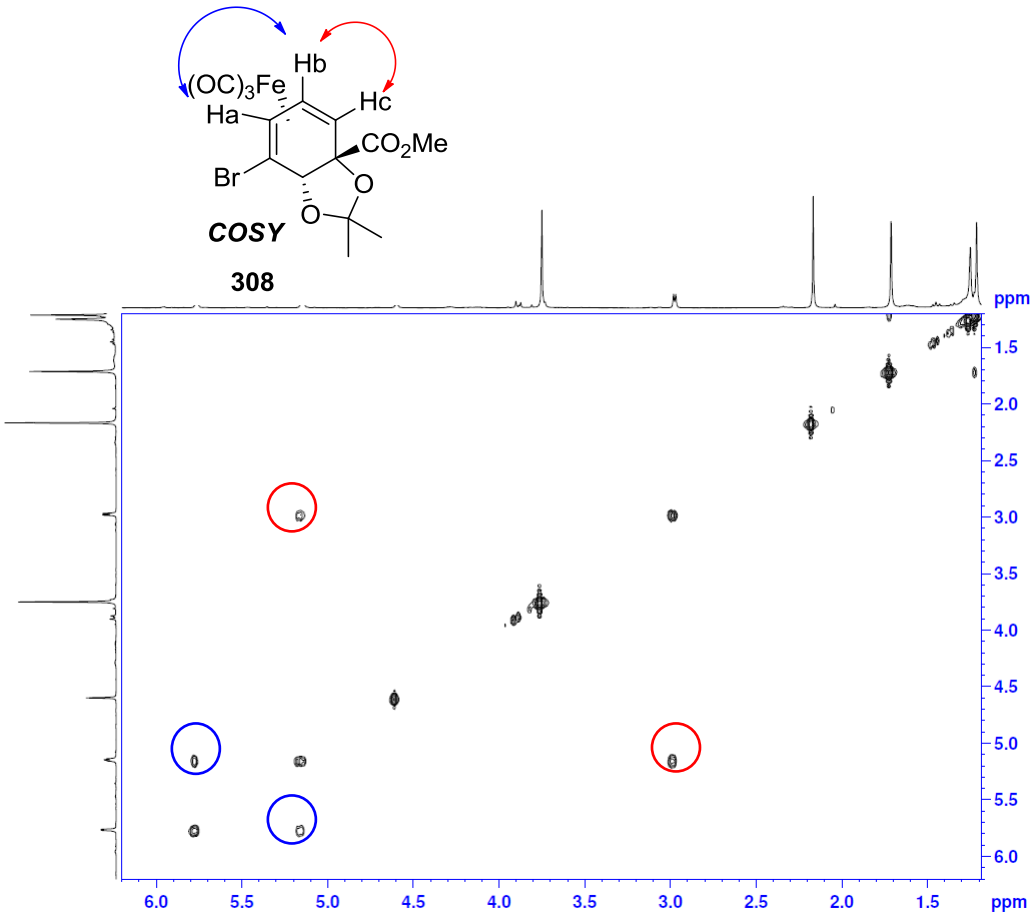
307

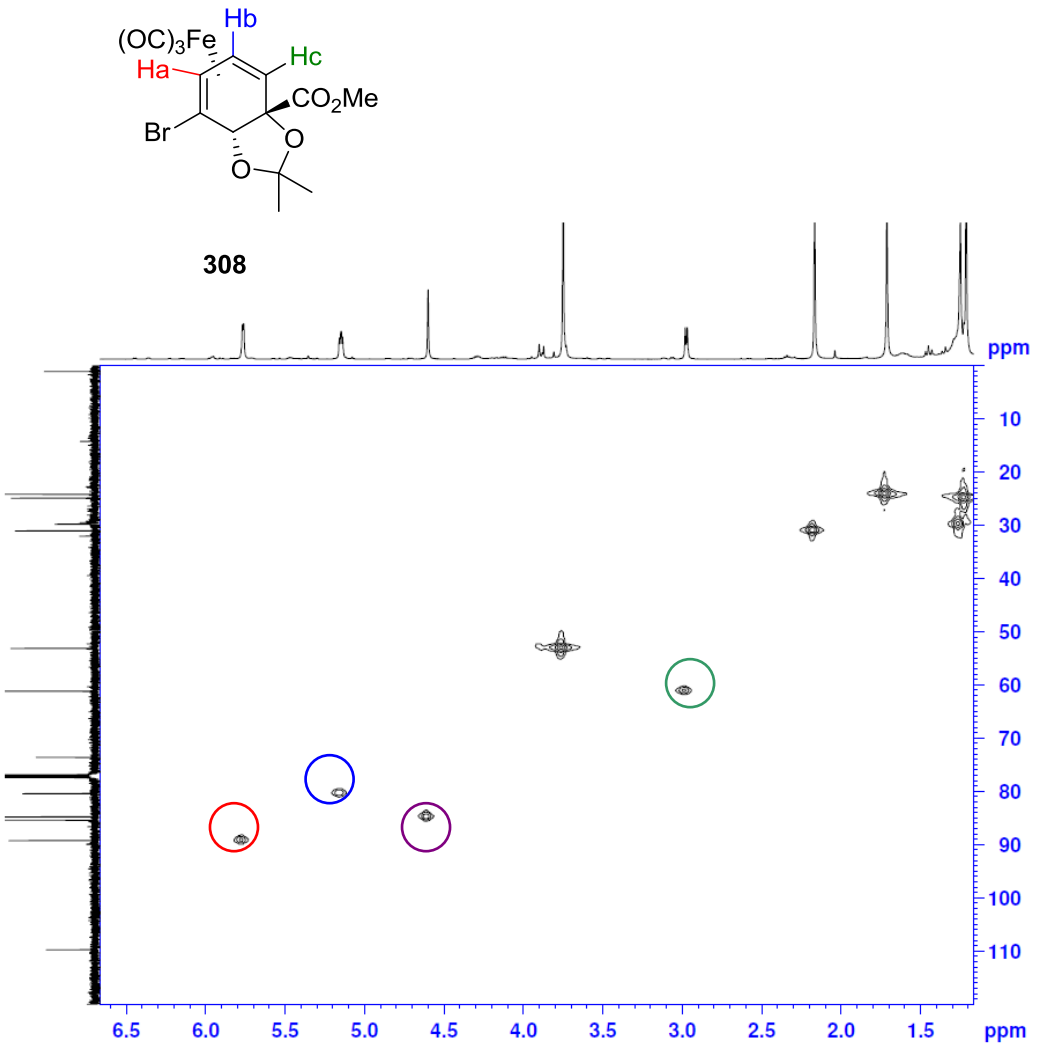

(OC)3Fe
Br
COOMe
O
O
Me
Me

307 *HMQC*

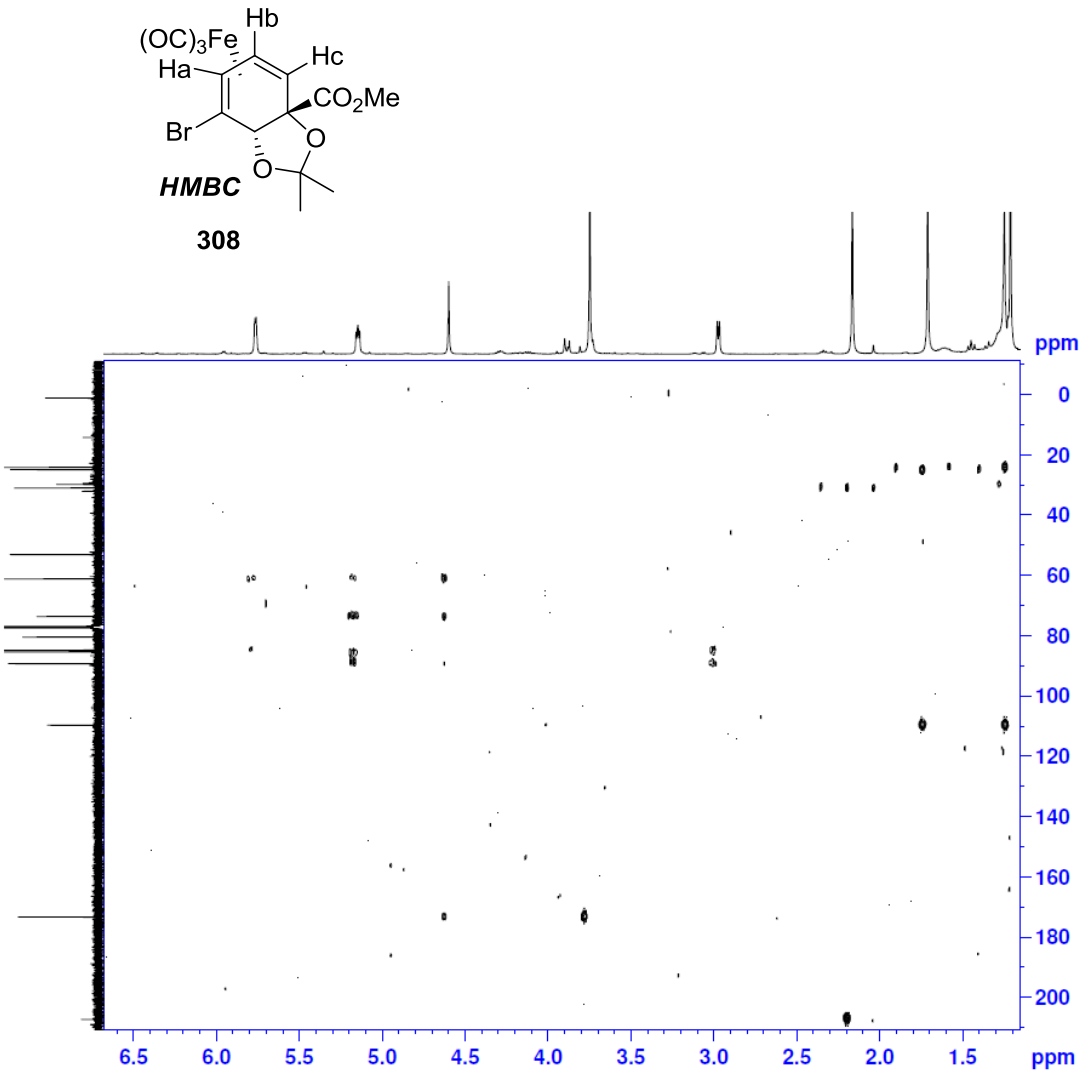

ppm
30
40
50
60
70
80
90
100
110
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

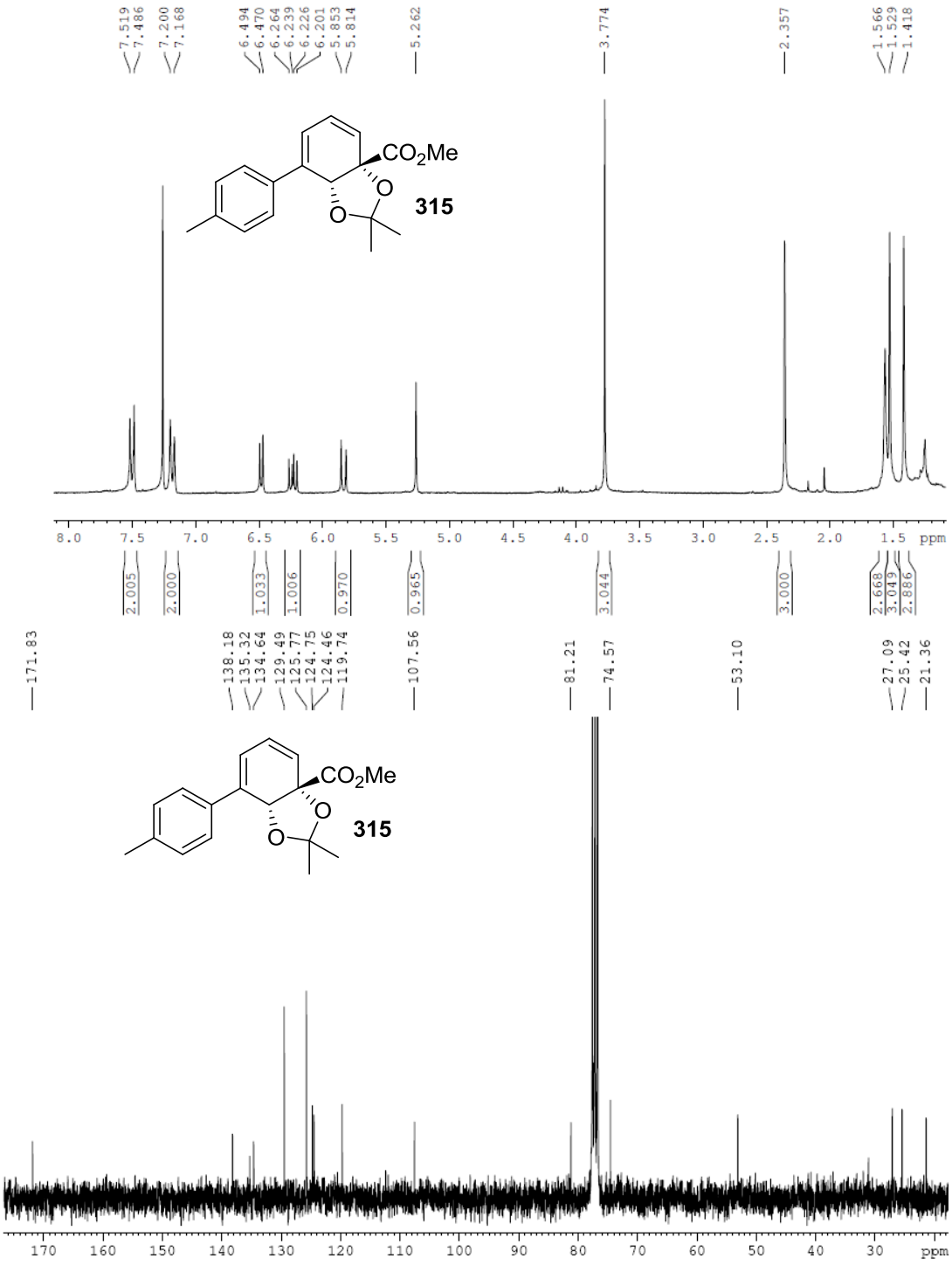

5.767
5.760
5.157
5.148
5.145
5.136
4.598
3.749
2.981
2.968
2.166
1.711
(OC)3Fe
Br
COOMe
O
O
Me
Me
308
1.000
0.983
0.932
3.087
0.930
3.023
3.199
207.09
173.28
109.73
89.27
85.42
84.84
80.45
73.61
61.21
53.14
31.06
24.95
24.20
(OC)3Fe
Br
COOMe
O
O
Me
Me
308
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

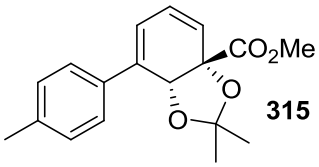

Hb
(OC)3Fe
Hc
Ha
CO2Me
Br
O
O
COSY
308
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Hb
(OC)3Fe
Ha
Hc
CO2Me
Br
O
O
ppm
10
20
30
40
50
60
70
80
90
100
110
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

308

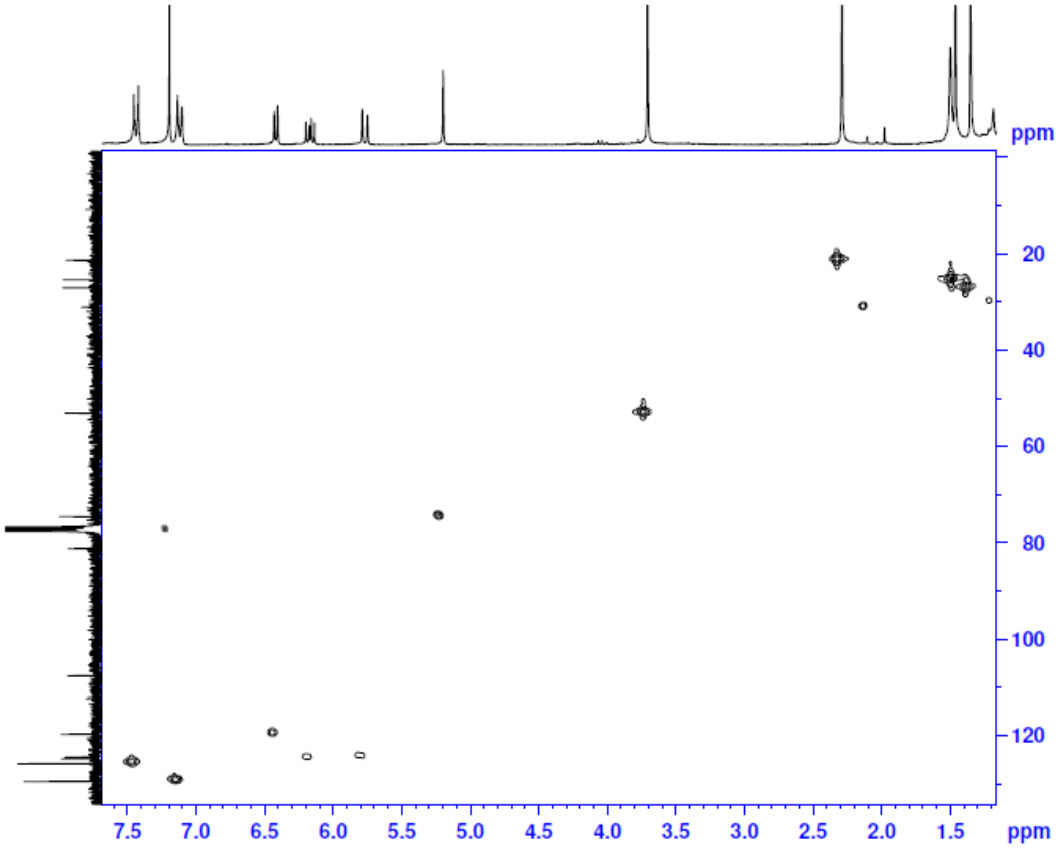

Hb
(OC)3Fe
Ha
Hc
CO2Me
Br
O
O
HMBC
308
ppm
0
20
40
60
80
100
120
140
160
180
200
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

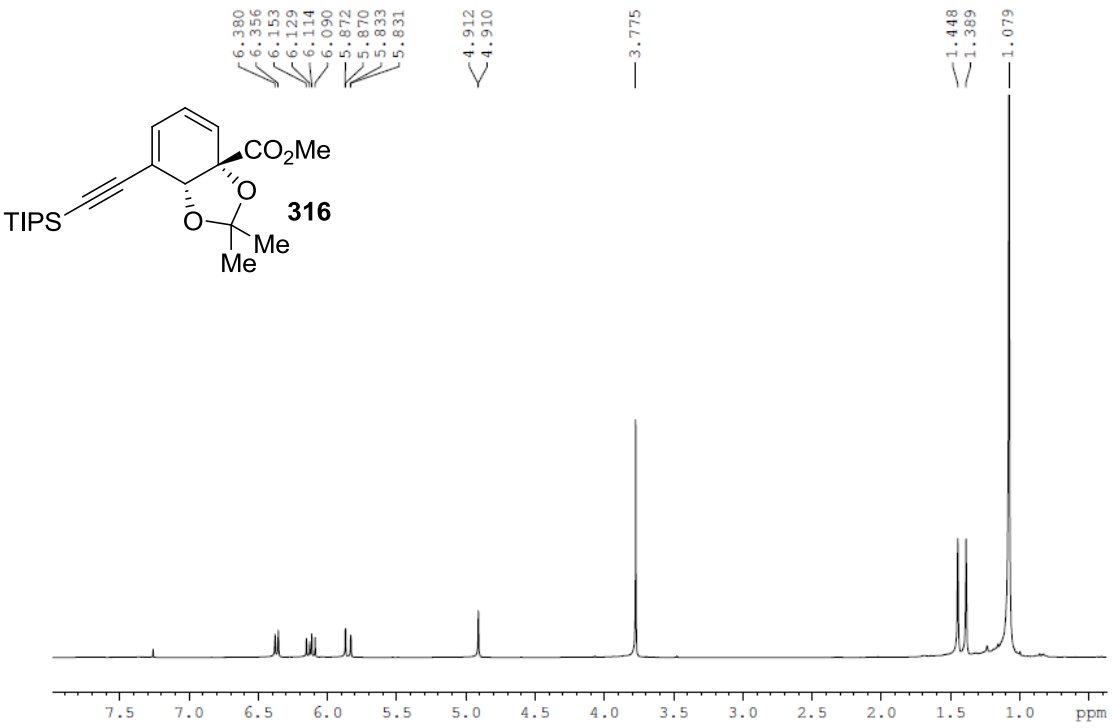

7.519
7.486
7.200
7.168
6.494
6.470
6.264
6.239
6.226
6.201
5.853
5.814
5.262
3.774
2.357
1.566
1.529
1.418
CO2Me
O
O
315
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.005
2.000
1.033
1.006
0.970
0.965
3.044
3.000
2.668
3.049
2.886
171.83
138.18
135.32
134.64
129.49
125.77
124.75
124.46
119.74
107.56
81.21
74.57
53.10
27.09
25.42
21.36
CO2Me
O
O
315
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

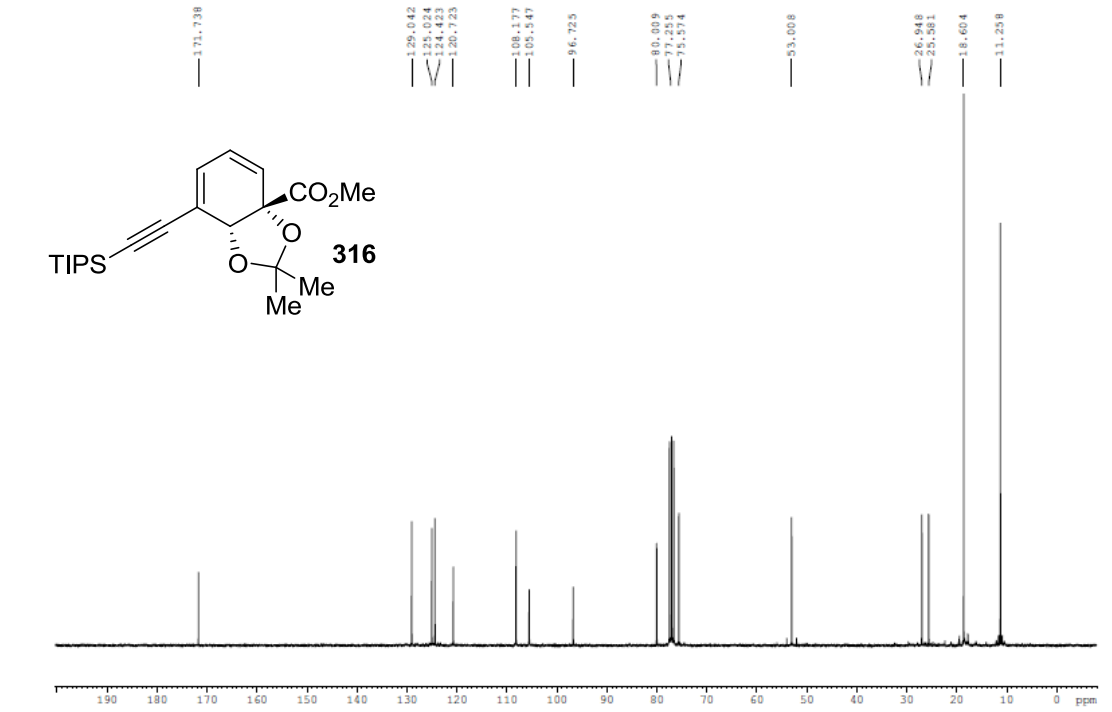

CO2Me
O
O

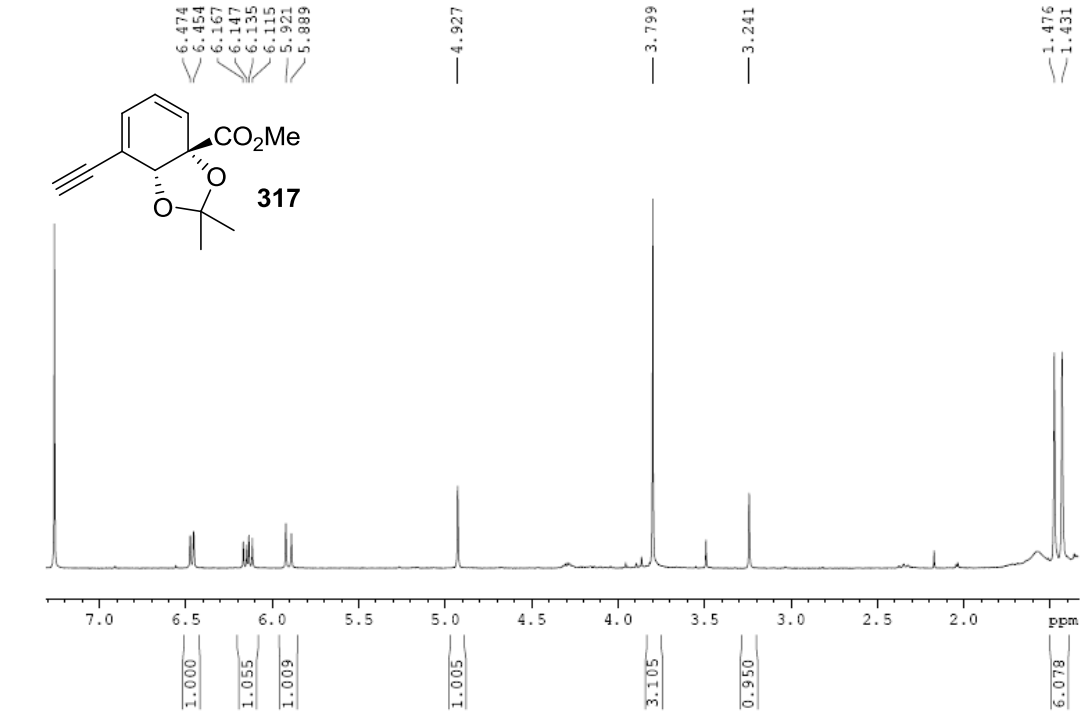
315

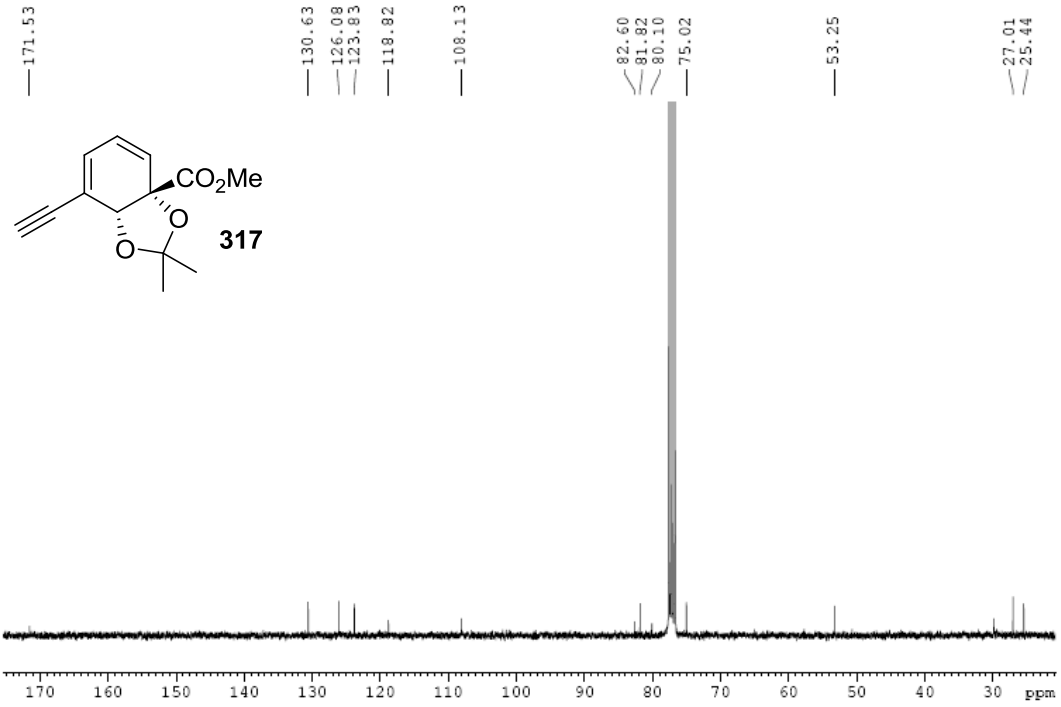
HMQC

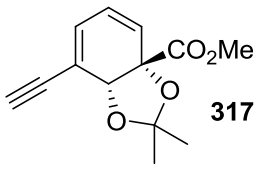

ppm
20
40
60
80
100
120
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


6.380
6.356
6.153
6.129
6.114
6.090
5.872
5.870
5.833
5.831
4.912
4.910
3.775
1.448
1.389
1.079
CO2Me
TIPS
O
O
Me
Me
316
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


171.738
129.042
125.024
124.423
120.723
108.177
105.547
96.725
80.009
77.255
75.574
53.008
26.948
25.581
18.604
11.238
CO2Me
TIPS
O
O
Me
Me
316
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

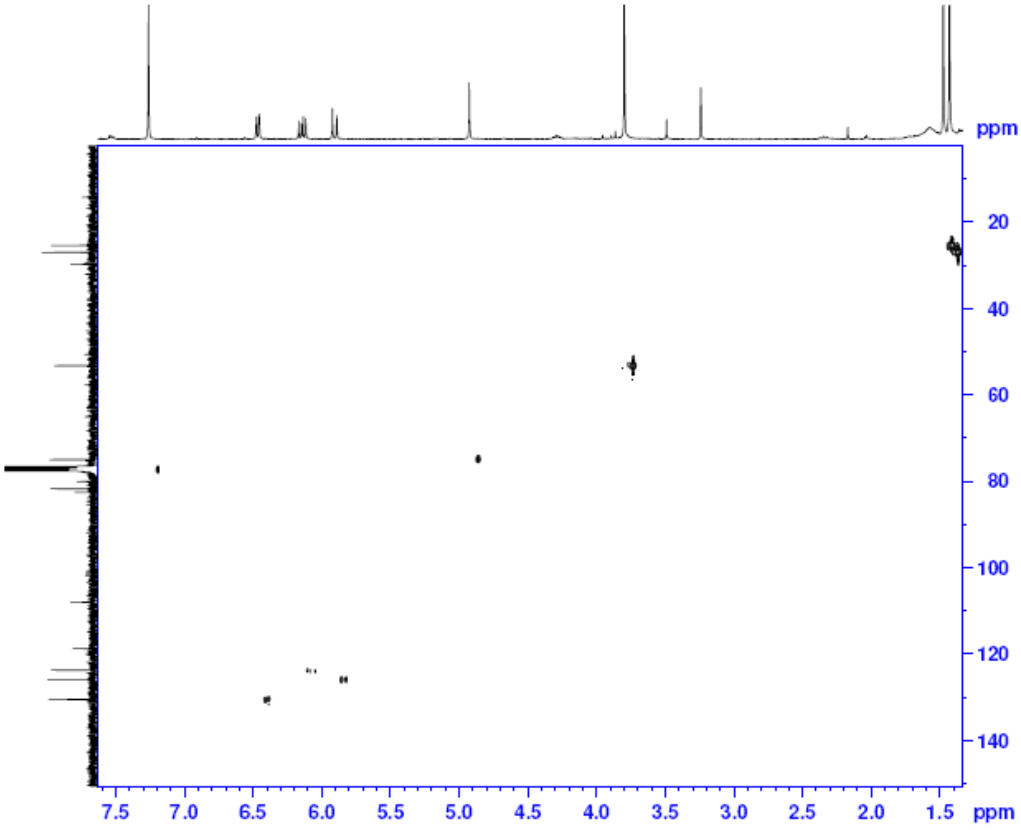

6.474
6.454
6.167
6.147
6.135
6.115
5.921
5.889
4.927
3.799
3.241
1.476
1.431
CO2Me
O
O
317
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.000
1.055
1.009
1.005
3.105
0.950
6.078

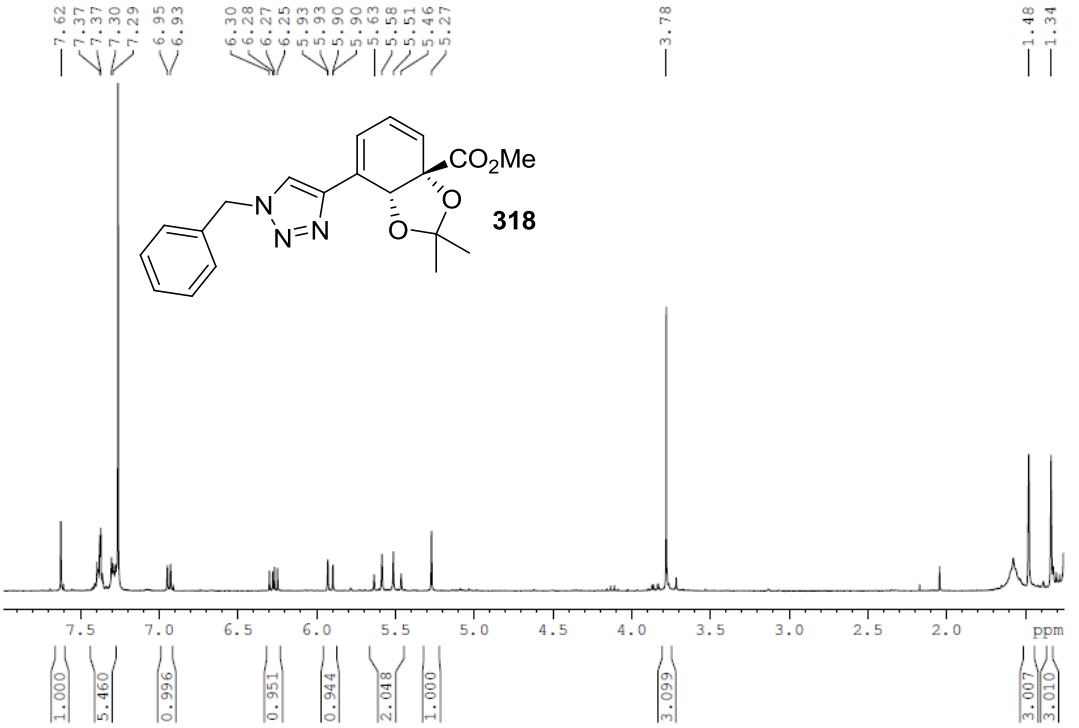

171.53
130.63
126.08
123.83
118.82
108.13
82.60
81.82
80.10
75.02
53.25
27.01
25.44
CO2Me
O
O
317
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

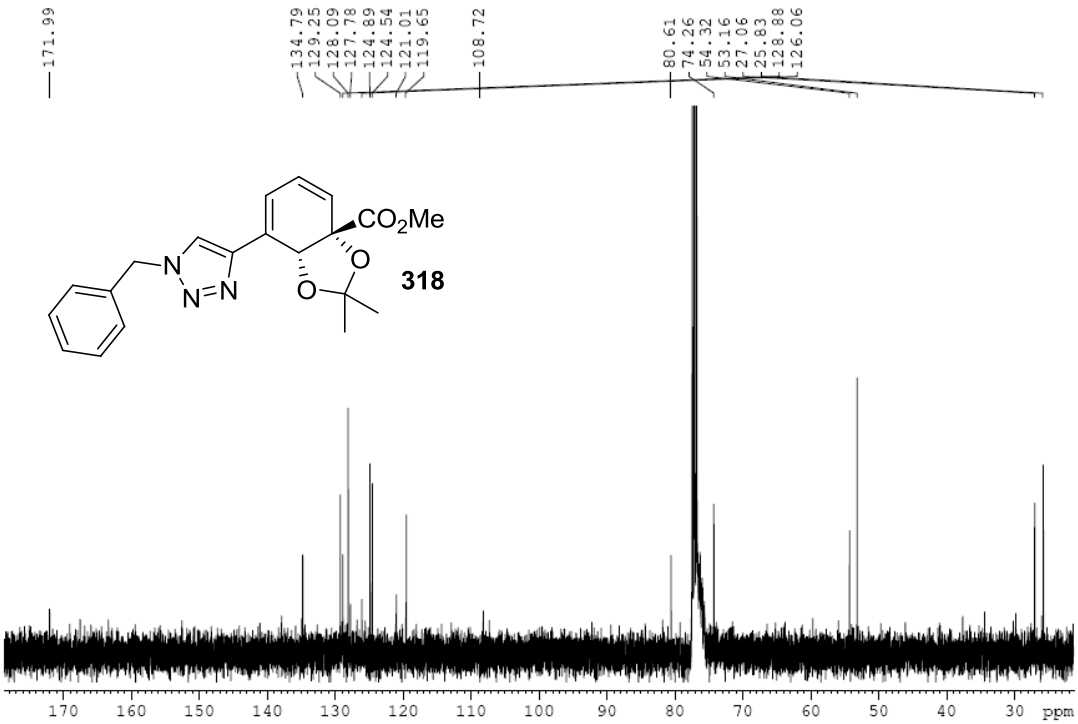

CO2Me
O
O

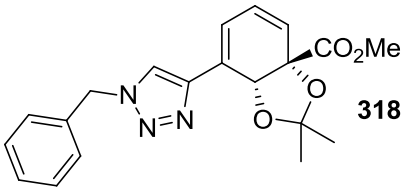
317

HMQC


ppm
20
40
60
80
100
120
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

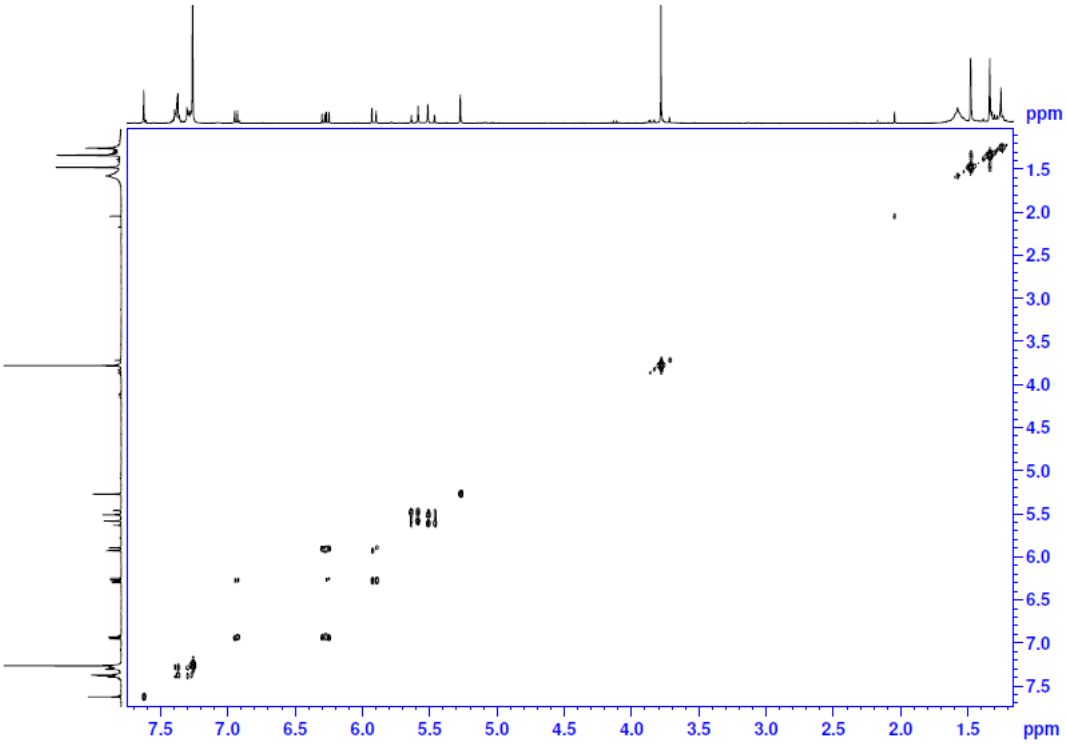

7.62
7.37
7.37
7.30
7.29
6.95
6.93
6.30
6.28
6.27
6.25
5.93
5.93
5.90
5.90
5.63
5.58
5.51
5.46
5.27
3.78
1.48
1.34
CO2Me
318
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.000
5.460
0.996
0.951
0.944
2.048
1.000
3.099
3.007
3.010

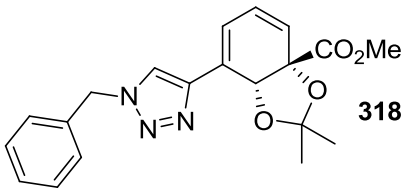

171.99
134.79
129.25
128.09
127.78
124.89
124.54
121.01
119.65
108.72
80.61
74.26
54.32
53.16
27.06
25.83
128.88
126.06
CO2Me
318
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


CO2Me
N
N=N
O
O

318

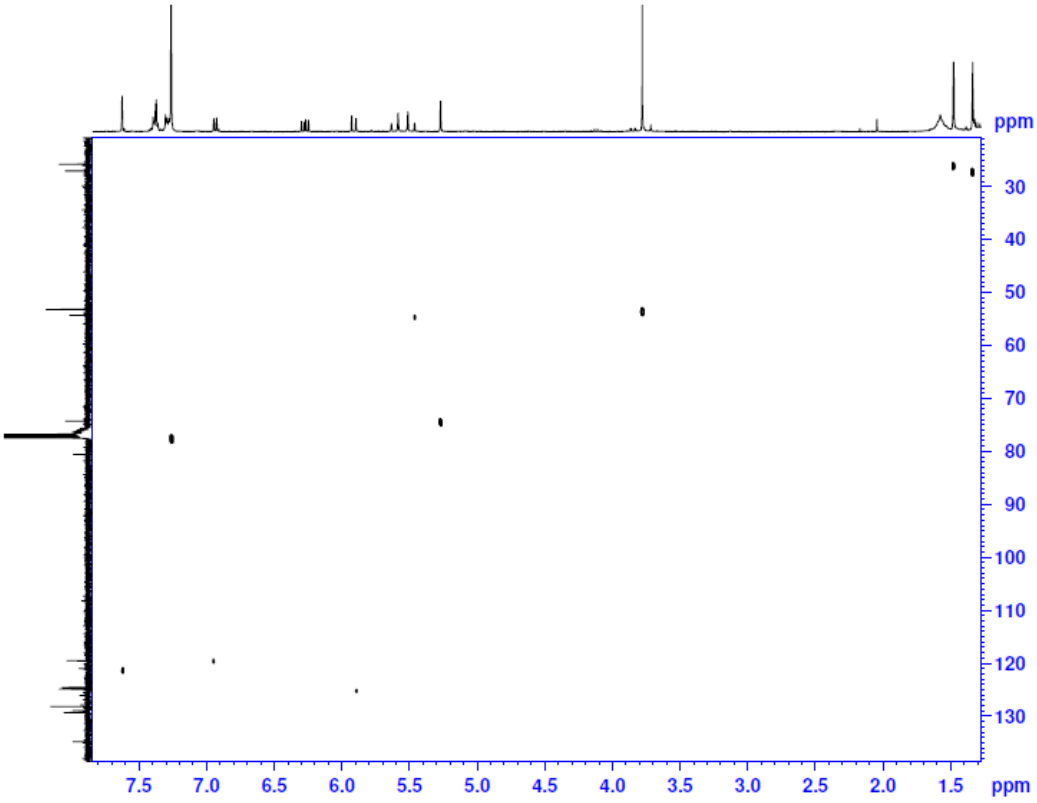
COSY

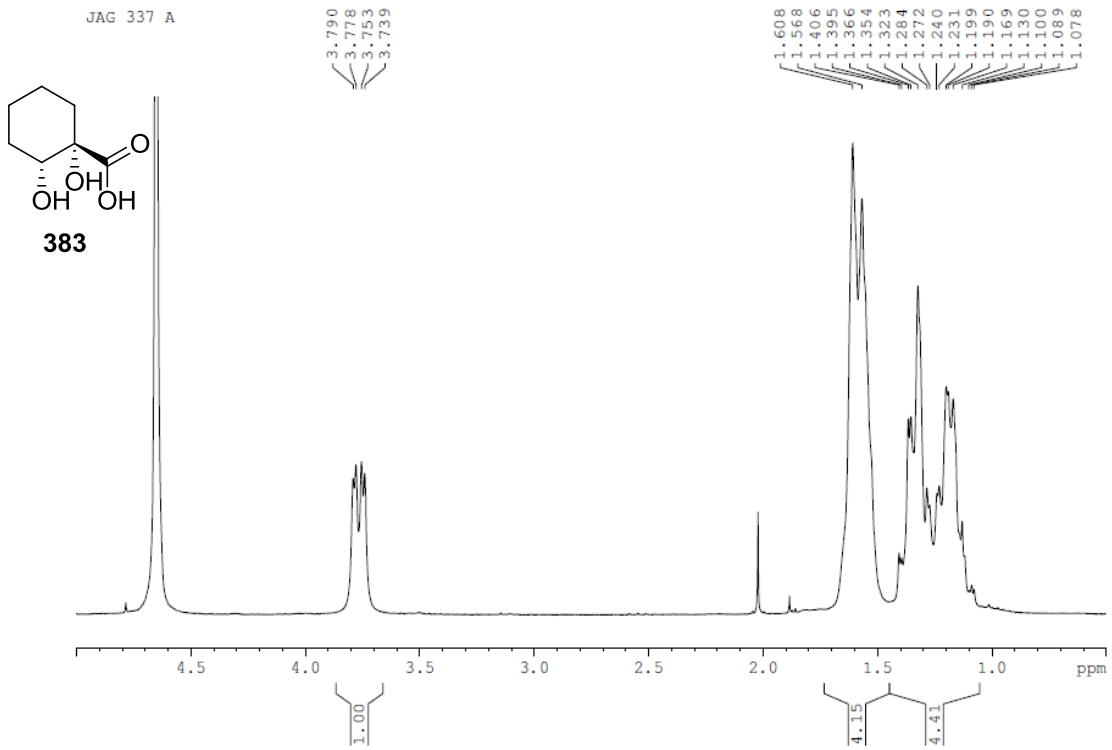

ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

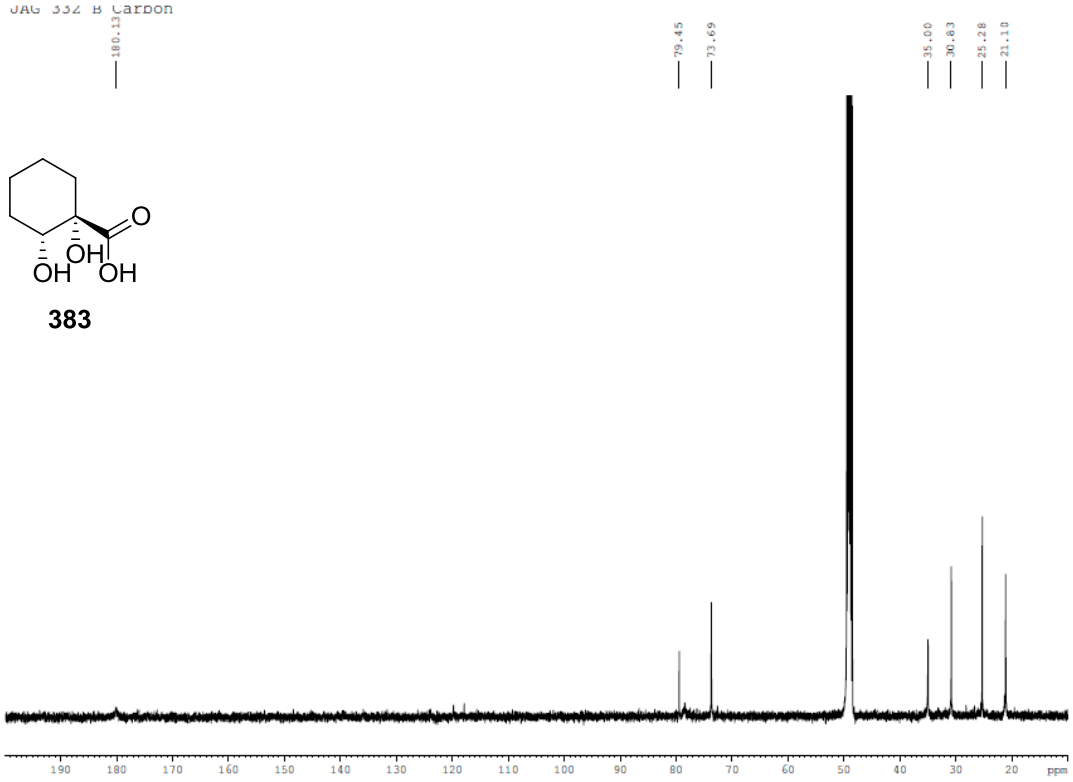

CO2Me
N
N=N
O
O

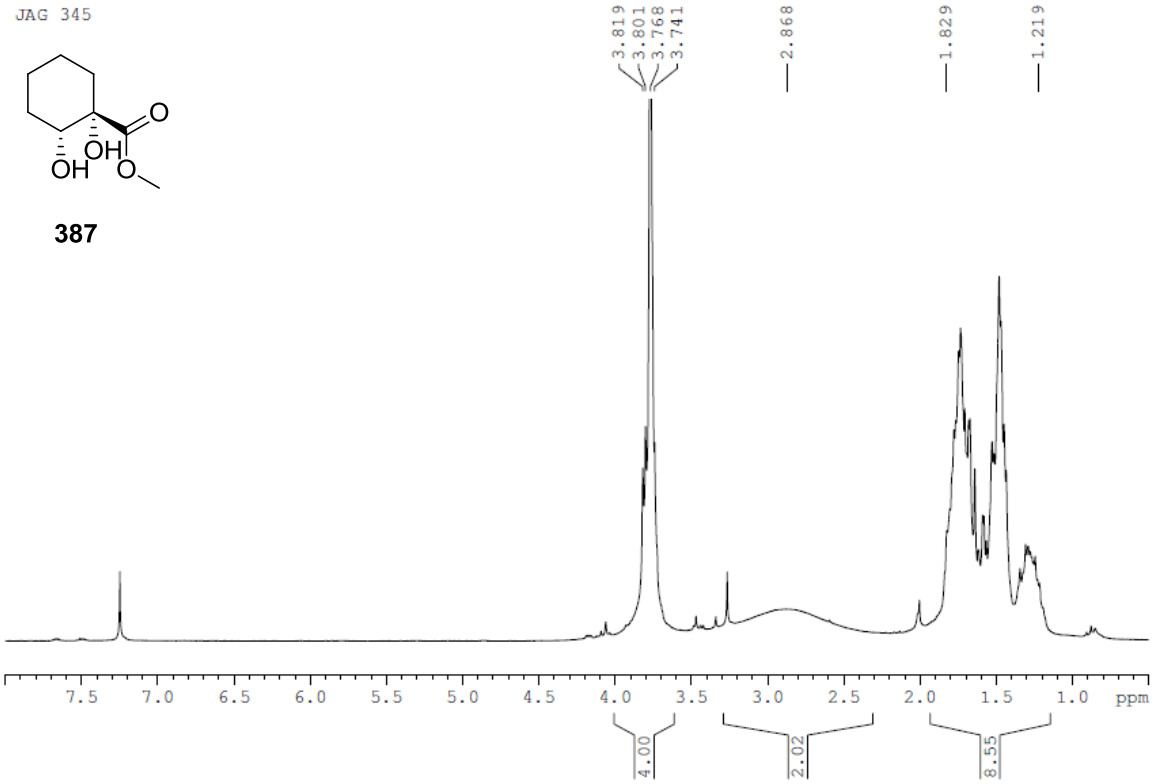
318

HSQC

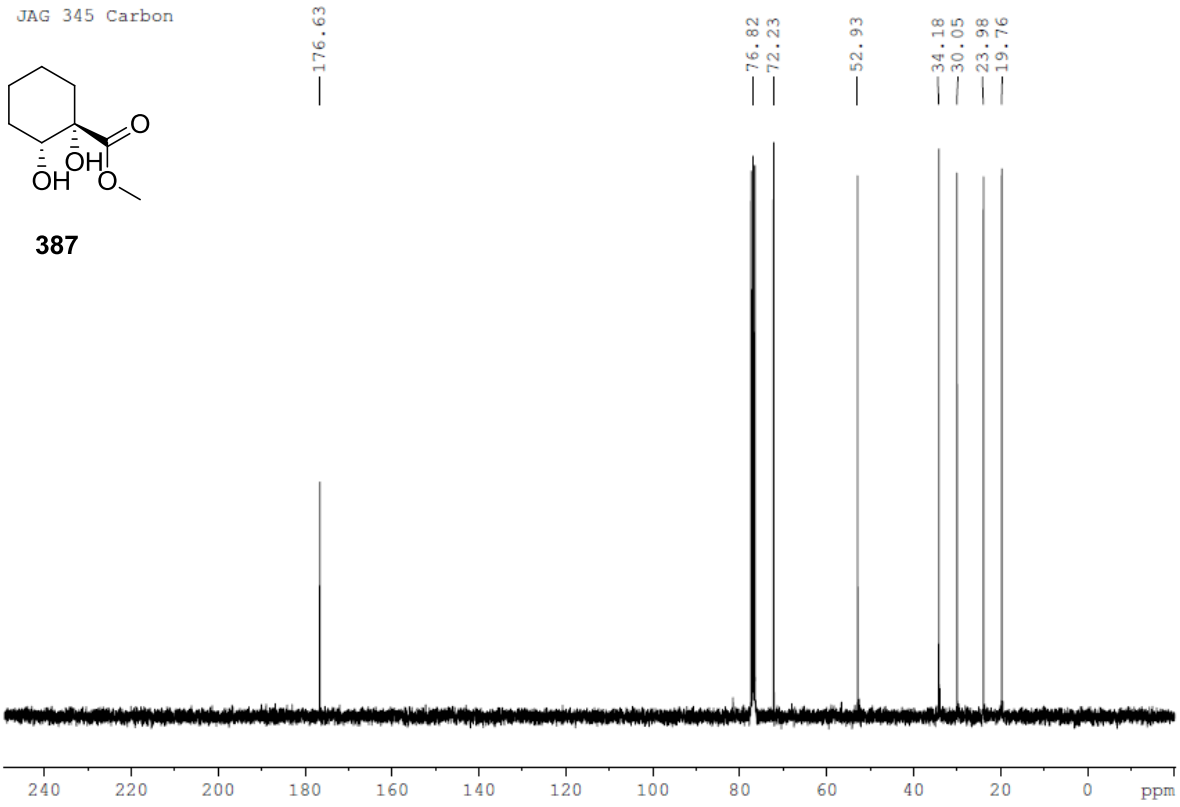

ppm
30
40
50
60
70
80
90
100
110
120
130
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


JAG 337 A
3.790
3.778
3.753
3.739
1.608
1.568
1.406
1.395
1.366
1.354
1.323
1.284
1.272
1.240
1.231
1.199
1.190
1.169
1.130
1.100
1.089
1.078
OH
OH
OH
O
383
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
4.15
4.41

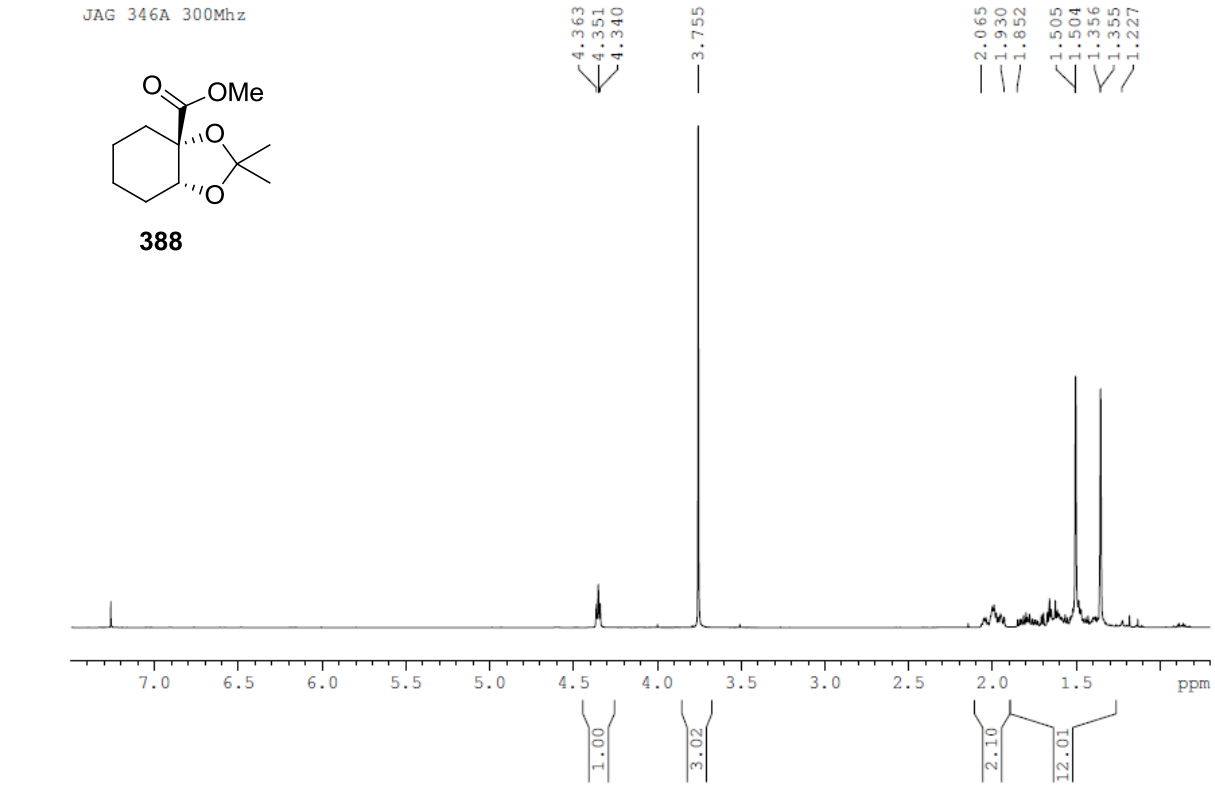

JAG 332 B Carbon
180.13
79.45
73.69
35.00
30.83
25.28
21.10
OH
OH
OH
O
383
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

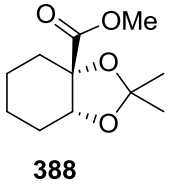

JAG 345
3.819
3.801
3.768
3.741
2.868
1.829
1.219
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
4.00
2.02
8.55

387


JAG 345 Carbon
176.63
76.82
72.23
52.93
34.18
30.05
23.98
19.76
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

387

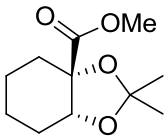

JAG 346A 300Mhz
4.363
4.351
4.340
3.755
2.065
1.930
1.852
1.505
1.504
1.356
1.355
1.227
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
3.02
2.10
12.01



388

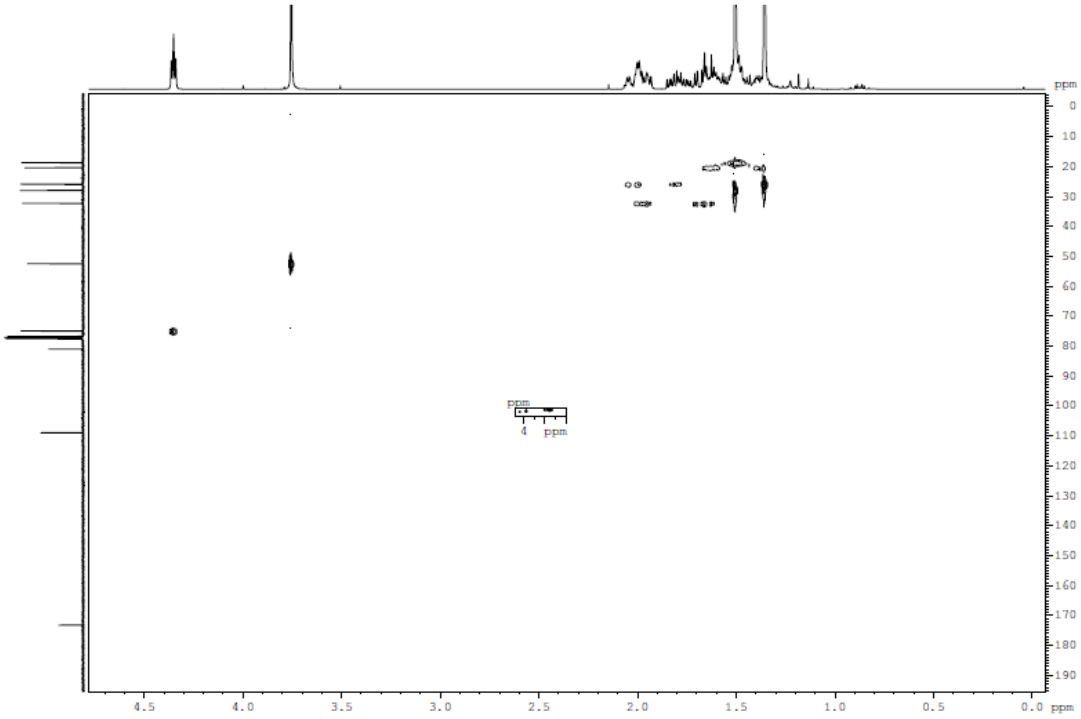
173.22
108.96
81.00
74.98
52.51
32.33
28.04
25.99
25.88
20.46
18.74
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

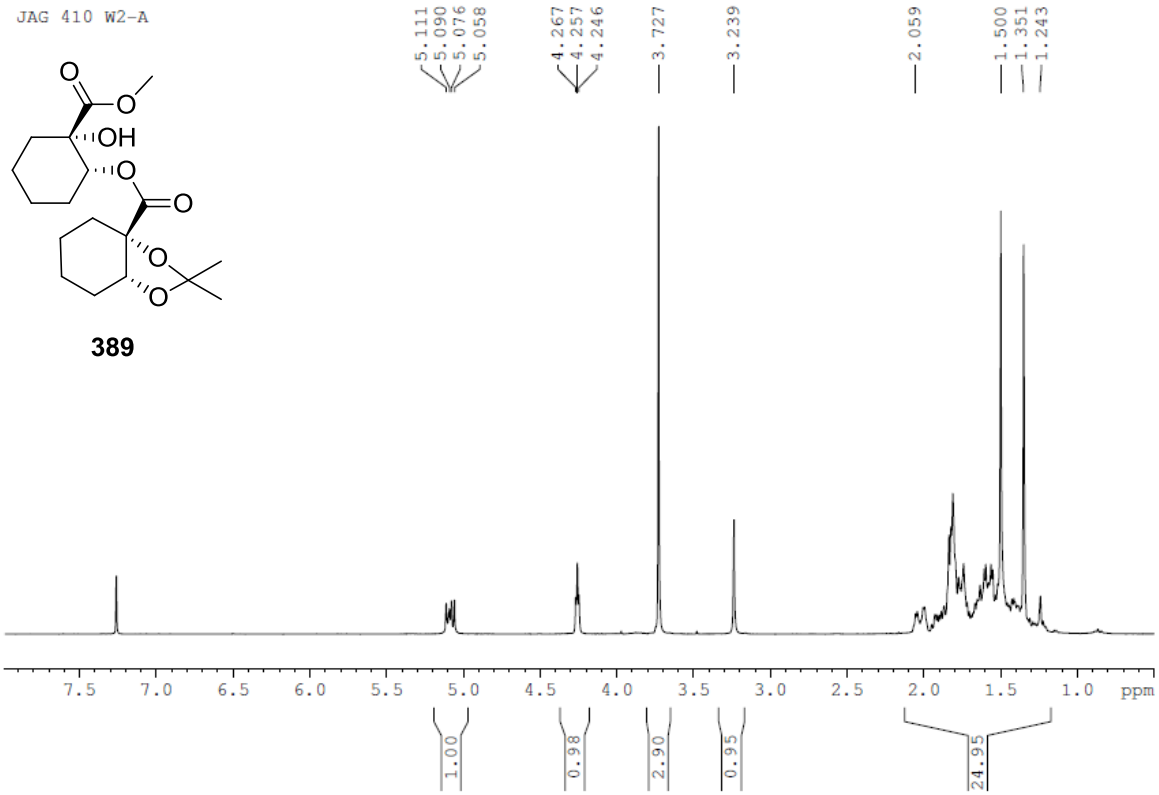
388



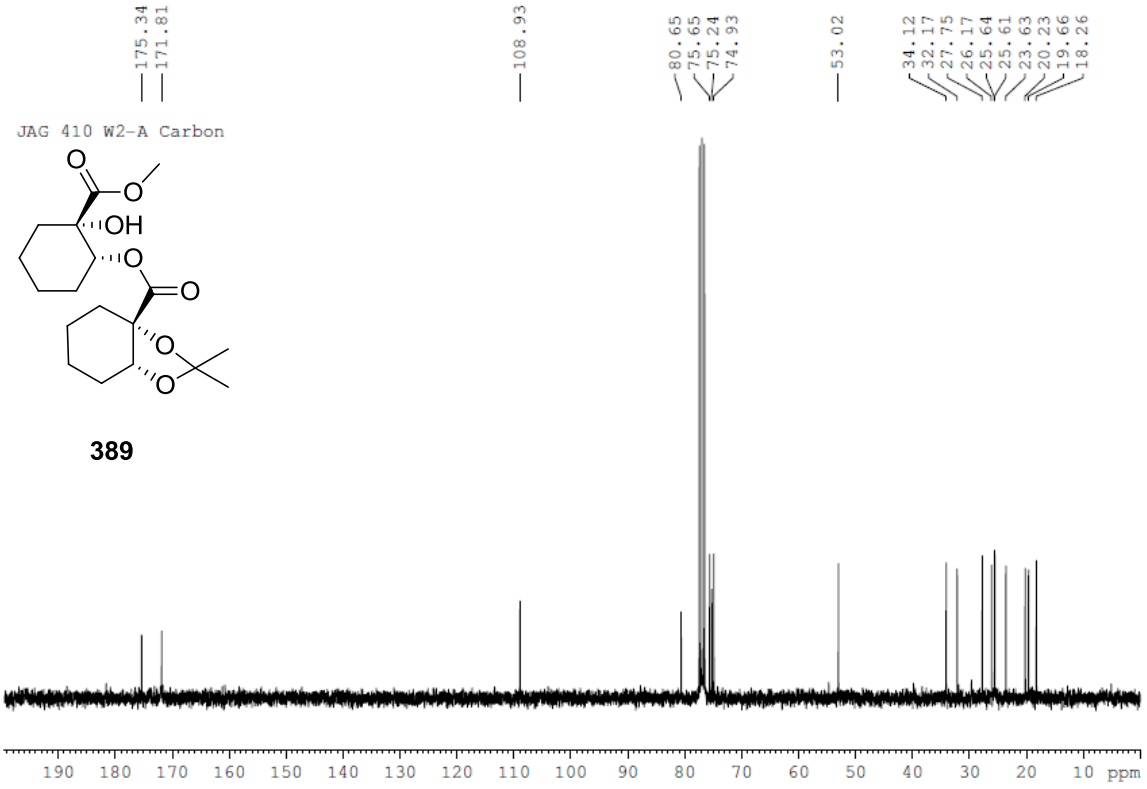
388
HSQC

JAG 346A HSQC



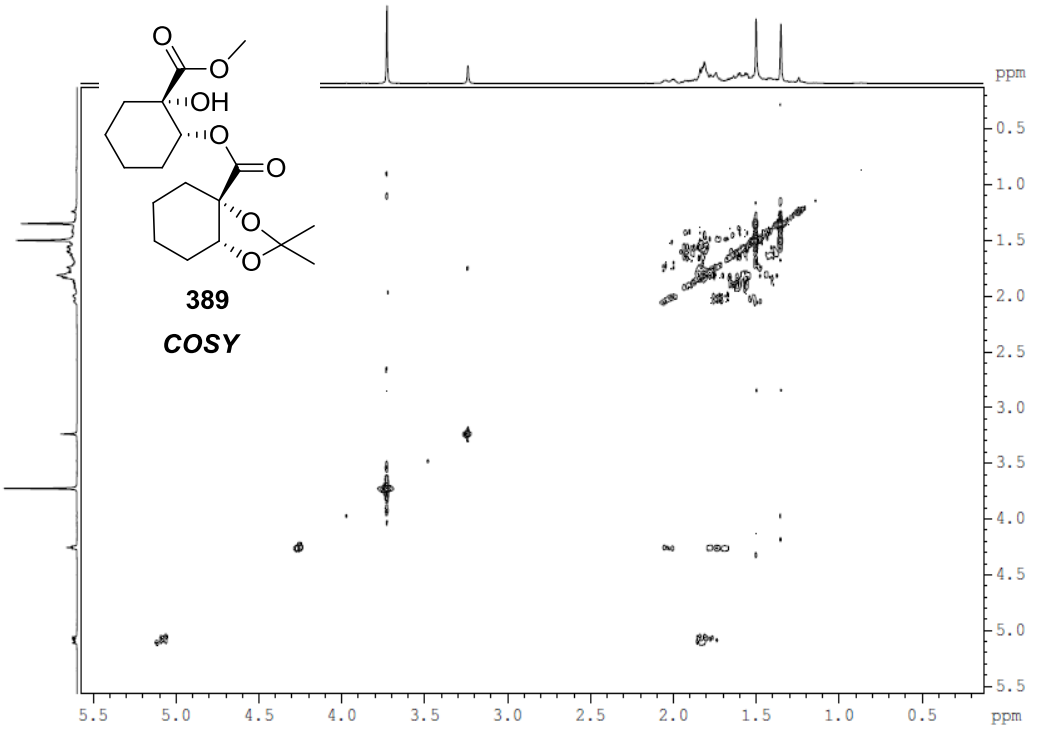

JAG 410 W2-A
5.111
5.090
5.076
5.058
4.267
4.257
4.246
3.727
3.239
2.059
1.500
1.351
1.243
OH
O
O
O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
0.98
2.90
0.95
24.95

389

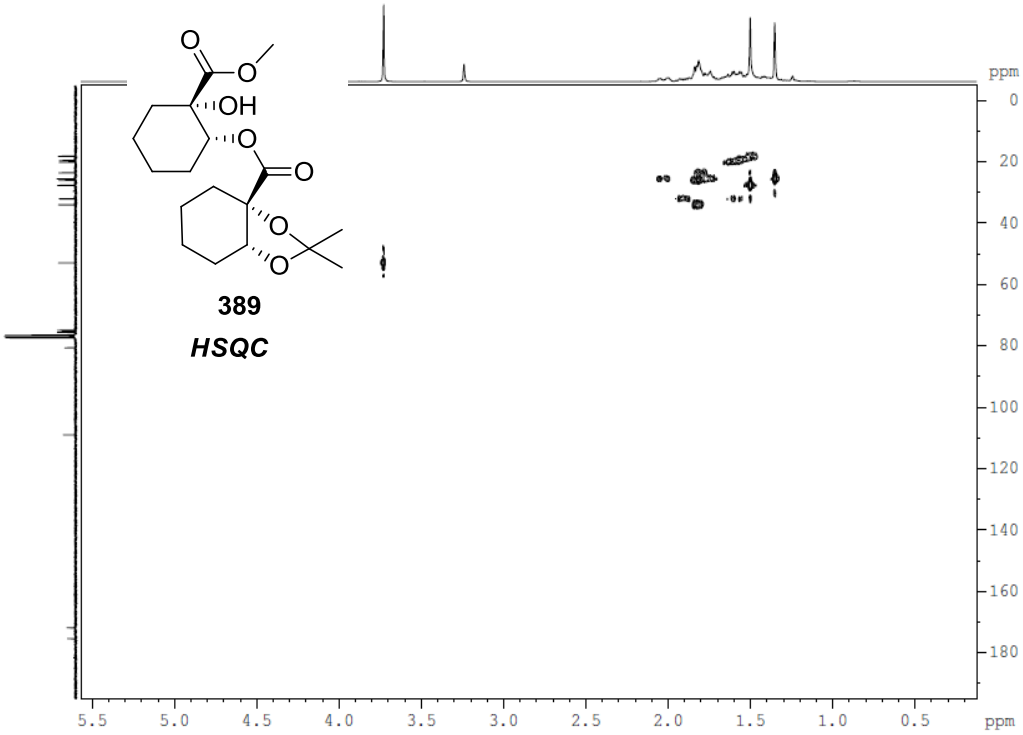

175.34
171.81
108.93
80.65
75.65
75.24
74.93
53.02
34.12
32.17
27.75
26.17
25.64
25.61
23.63
20.23
19.66
18.26
JAG 410 W2-A Carbon
OH
O
O
O
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

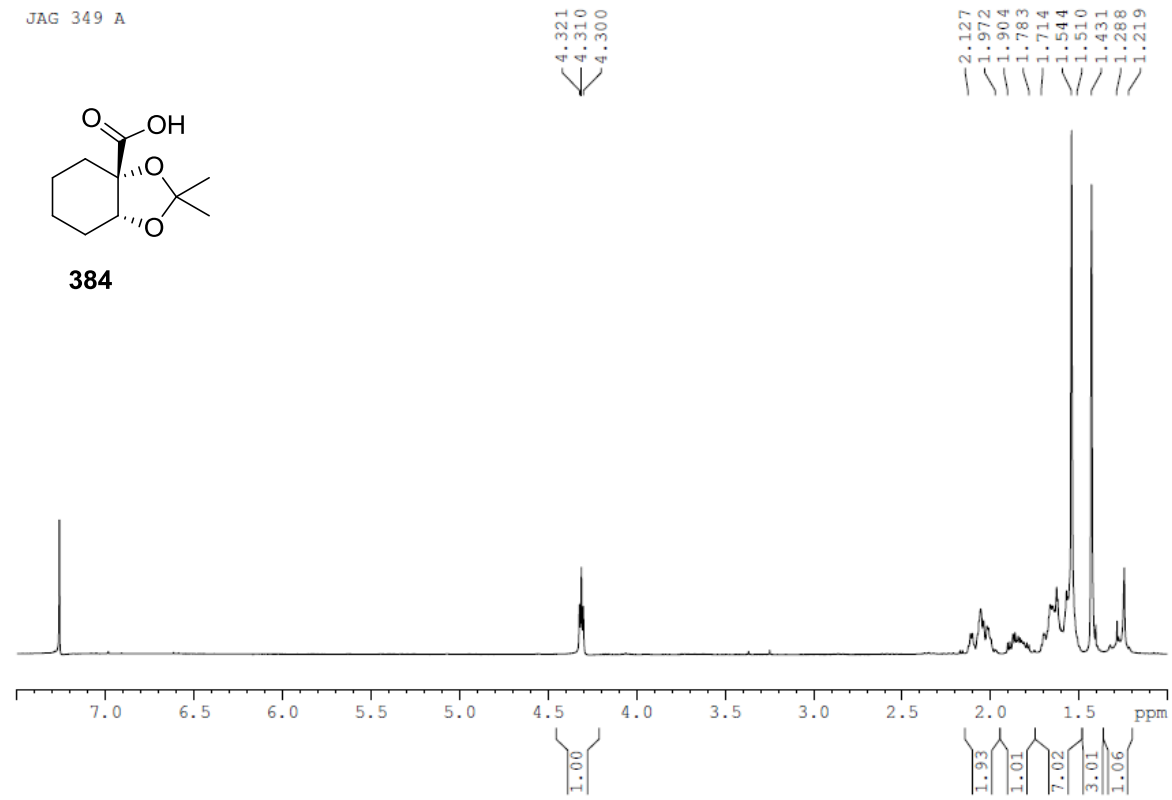
389

JAG 410 W2-A COSY

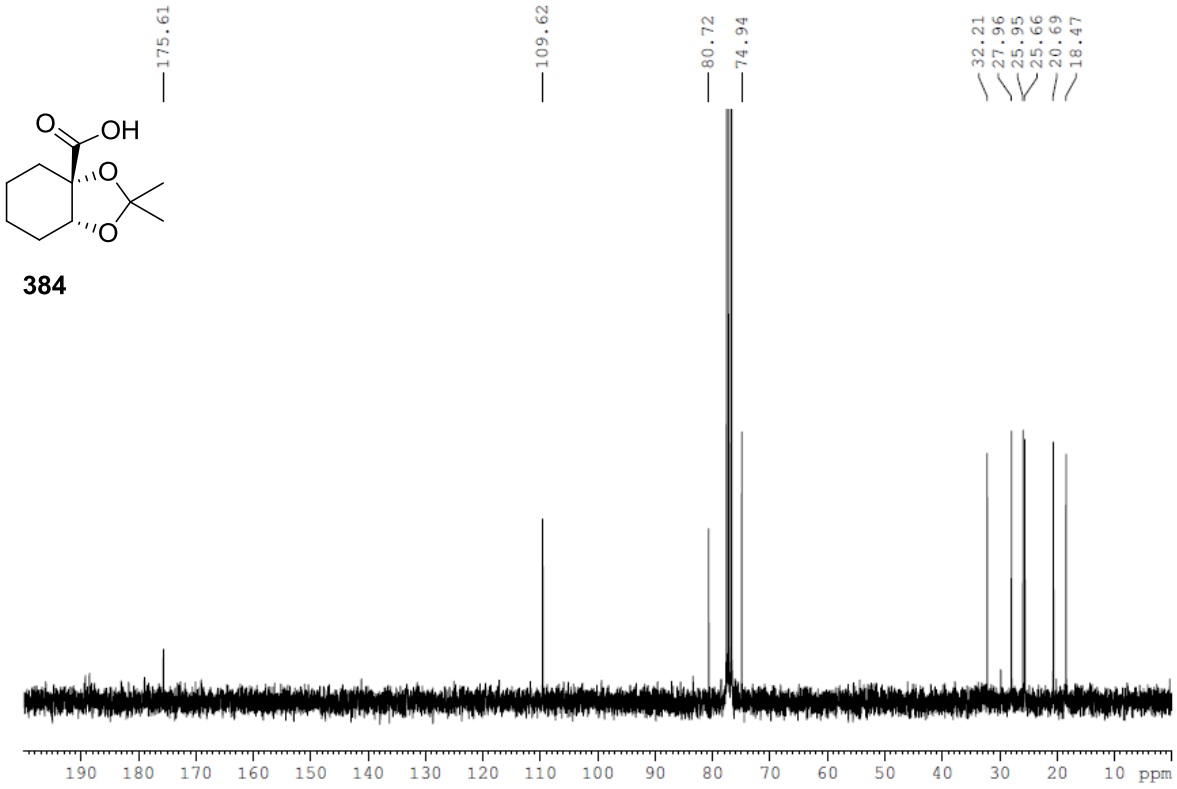


JAG 410 W2-A HSQC

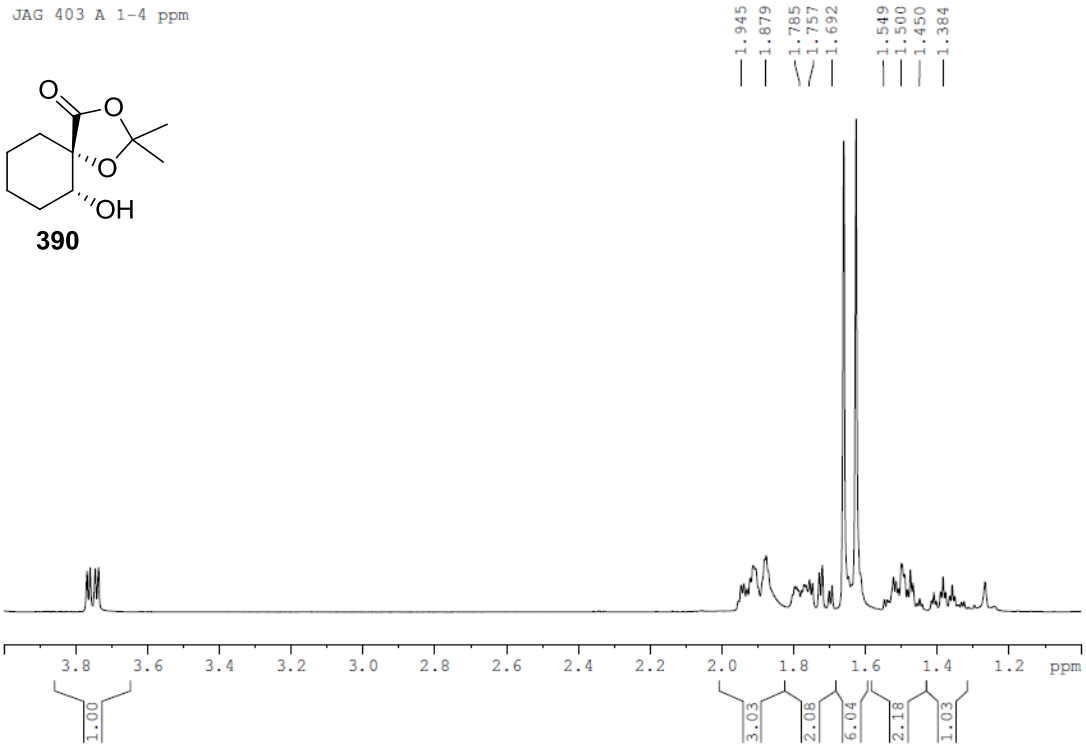



JAG 349 A
4.321
4.310
4.300
2.127
1.972
1.904
1.783
1.714
1.544
1.510
1.431
1.288
1.219
O
OH
O
O
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.93
1.01
7.02
3.01
1.06

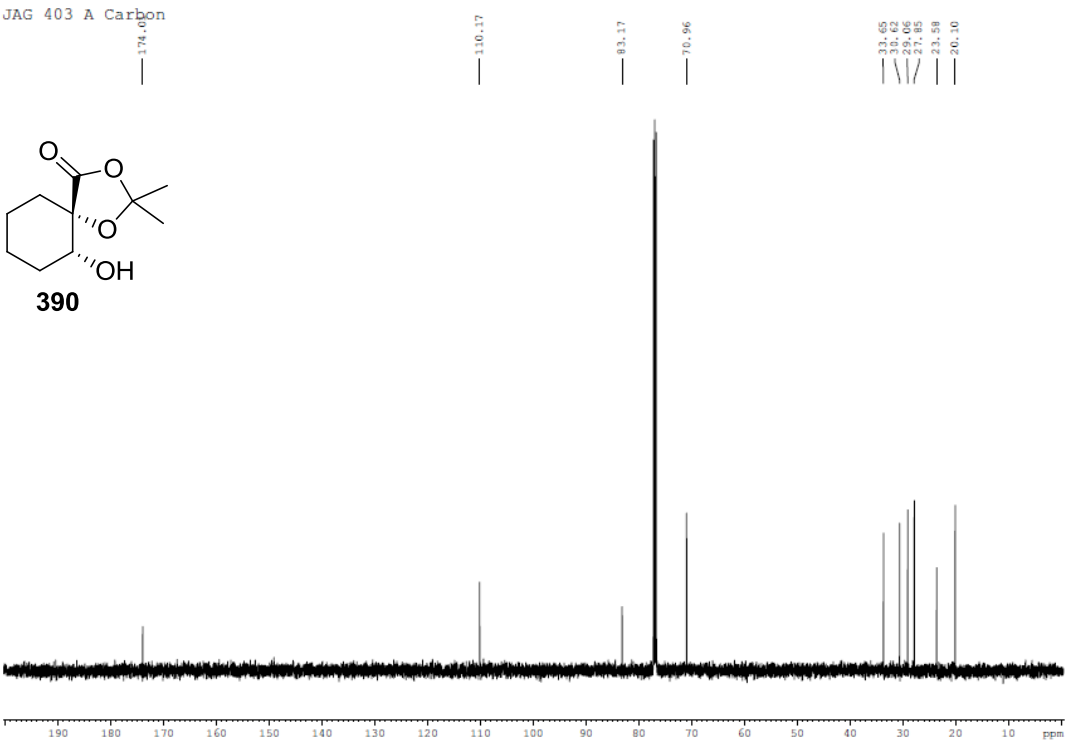
384


175.61
109.62
80.72
74.94
32.21
27.96
25.95
25.66
20.69
18.47
O
OH
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

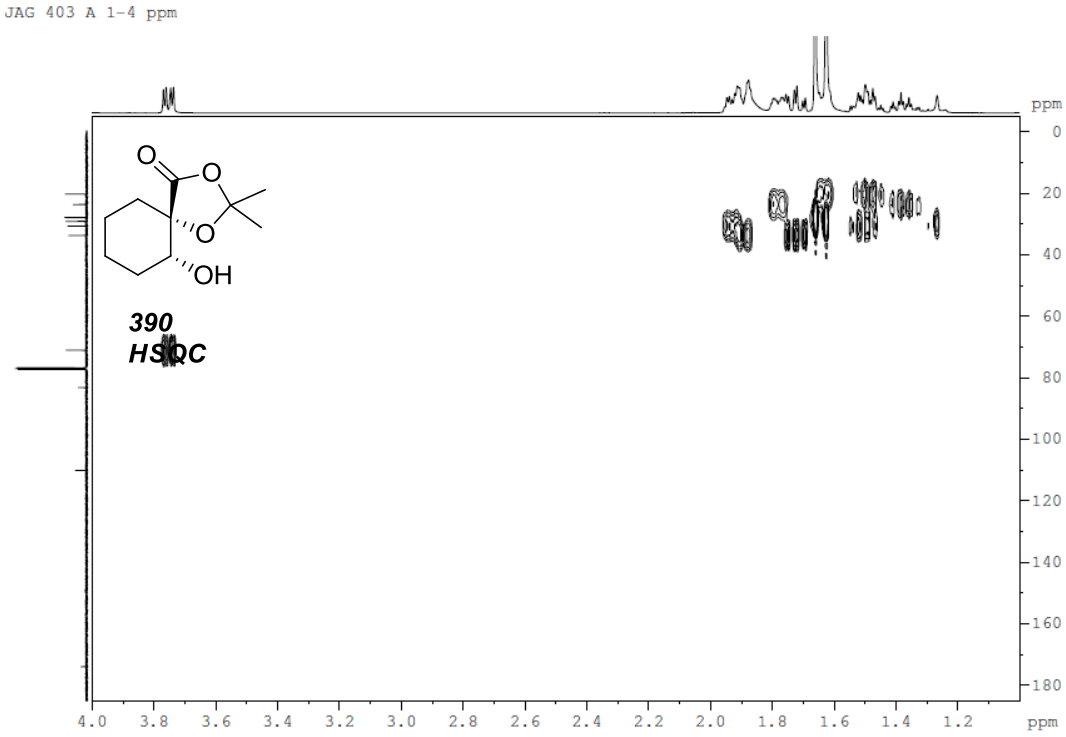
384

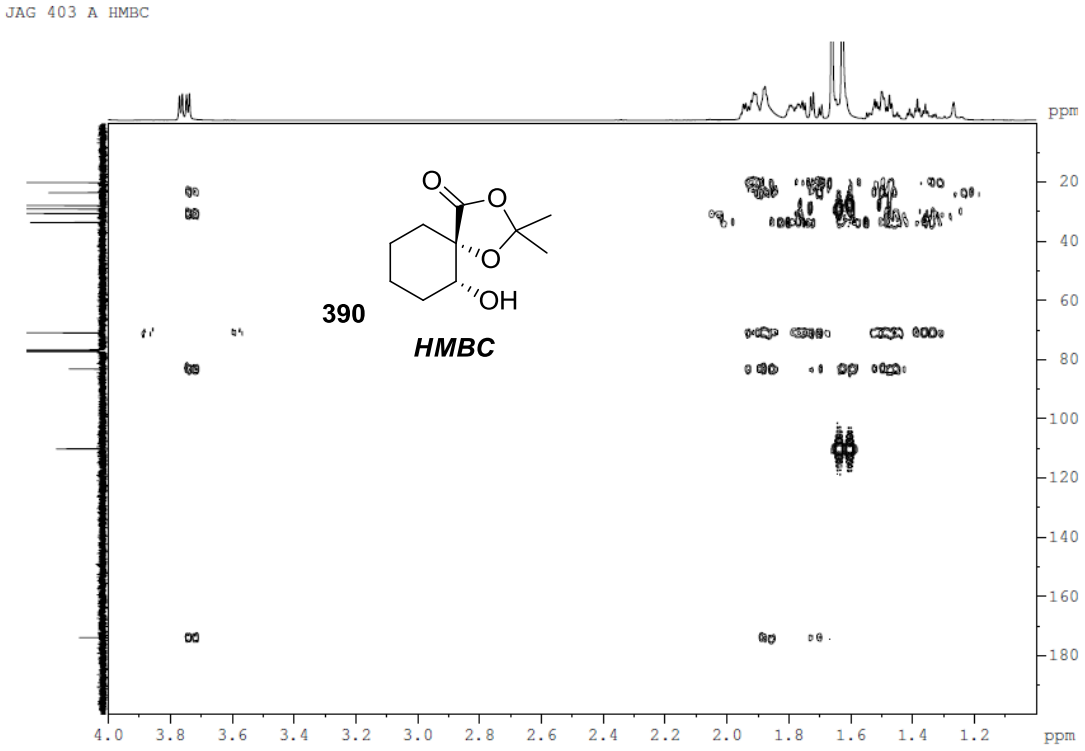

JAG 403 A 1-4 ppm
1.945
1.879
1.785
1.757
1.692
1.549
1.500
1.450
1.384
O
O
O
OH
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
ppm
1.00
3.03
2.08
6.04
2.18
1.03

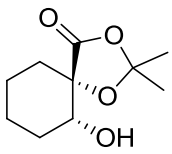
390


JAG 403 A Carbon
174.06
110.17
83.17
70.96
33.65
31.62
29.06
27.85
23.58
20.10
O
O
O
OH
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

390

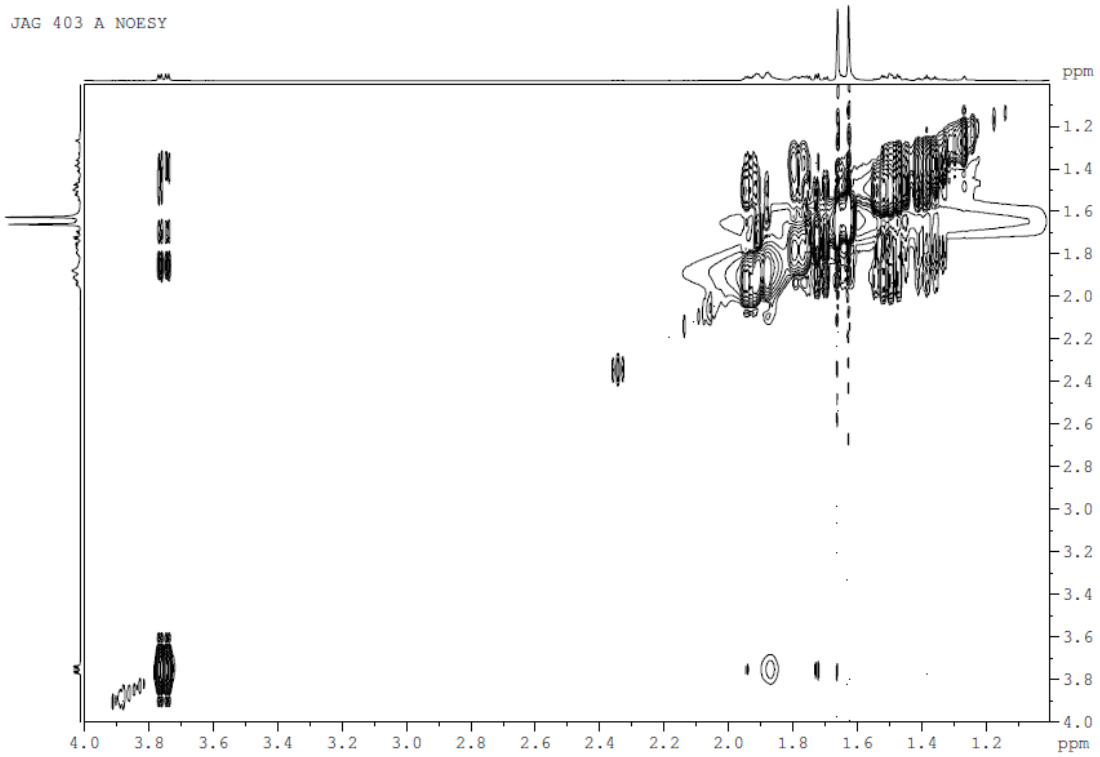

JAG 403 A 1-4 ppm
O
O
O
OH
390
HSQC
ppm
0
20
40
60
80
100
120
140
160
180
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
ppm

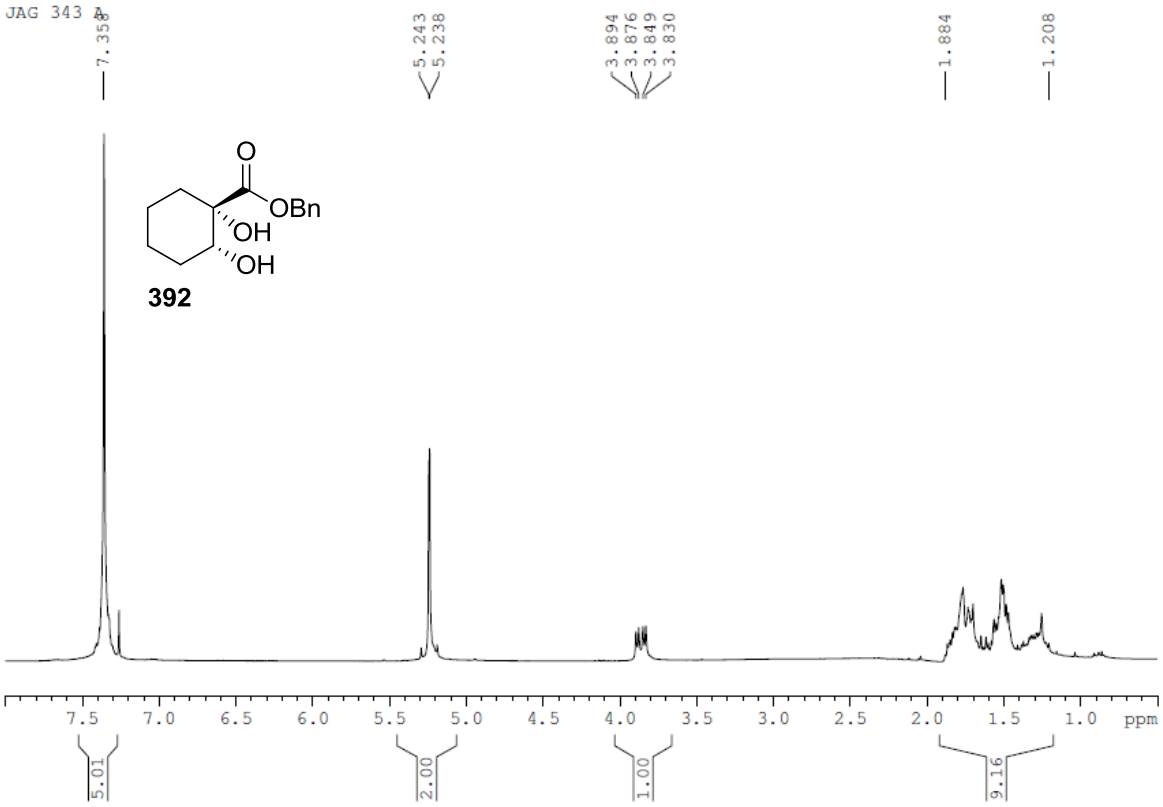

JAG 403 A HMBC
O
O
O
OH
390
HMBC
ppm
20
40
60
80
100
120
140
160
180
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
ppm

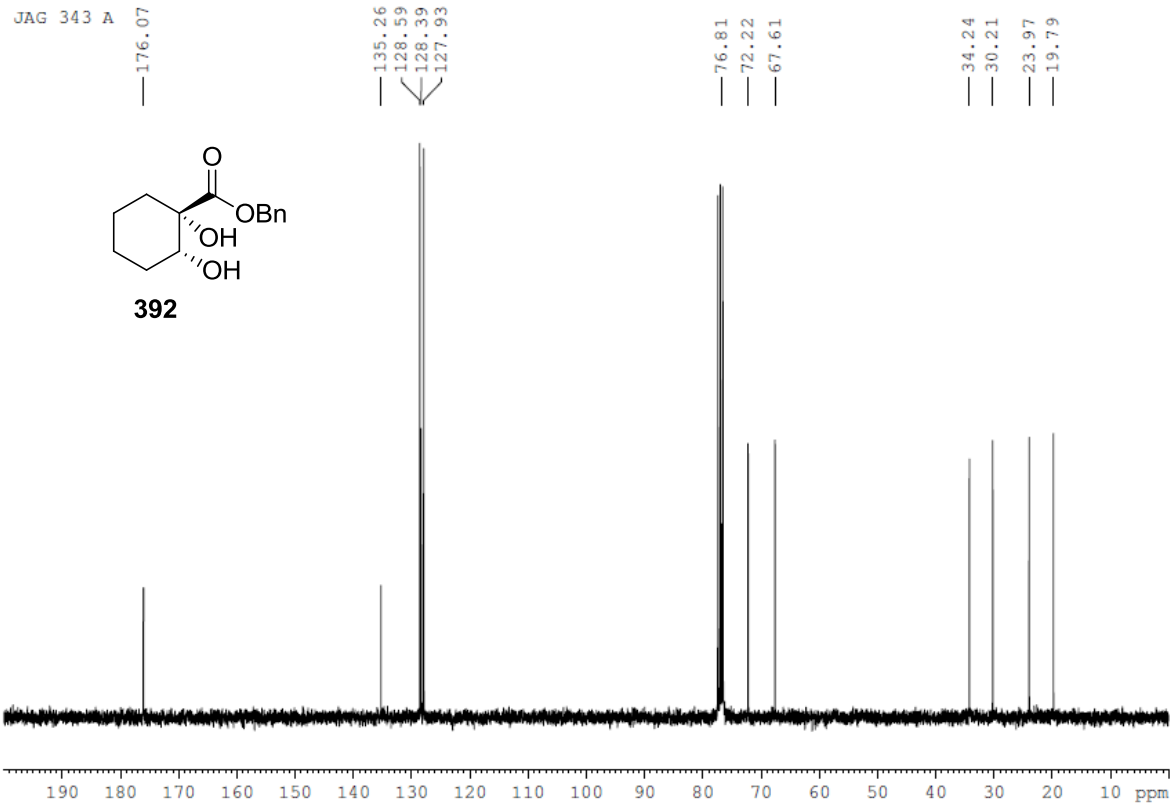

O
O
O
OH

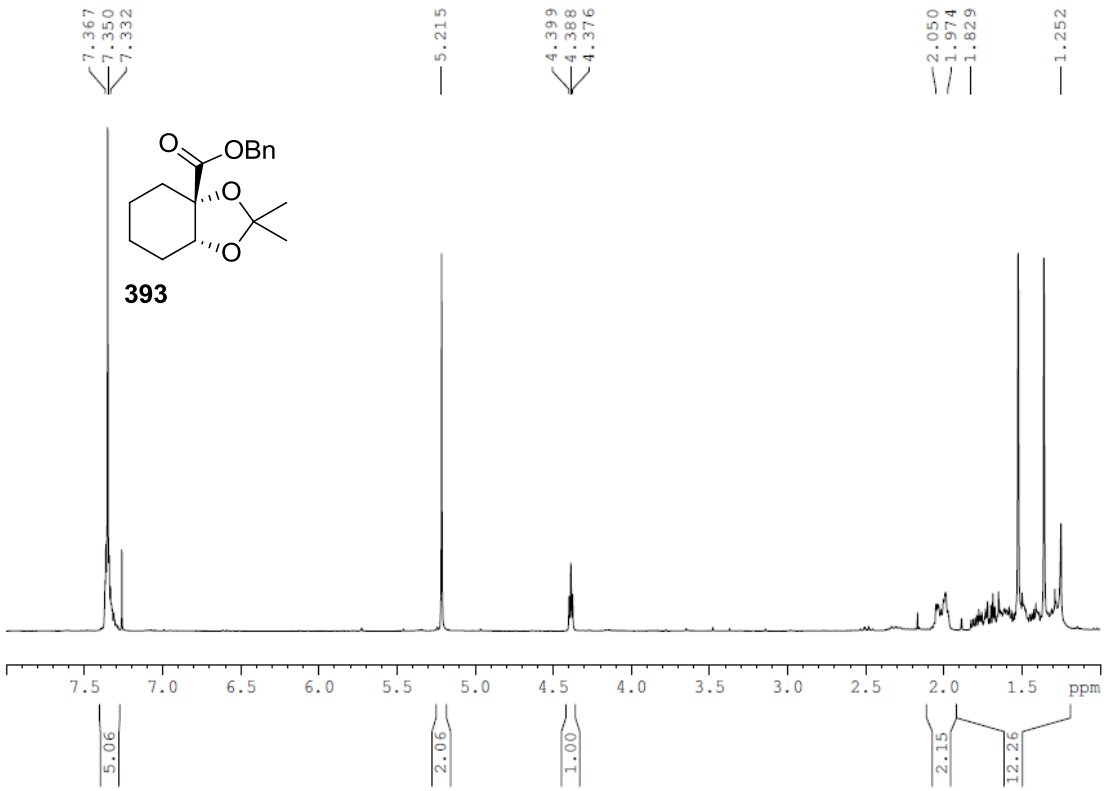
390

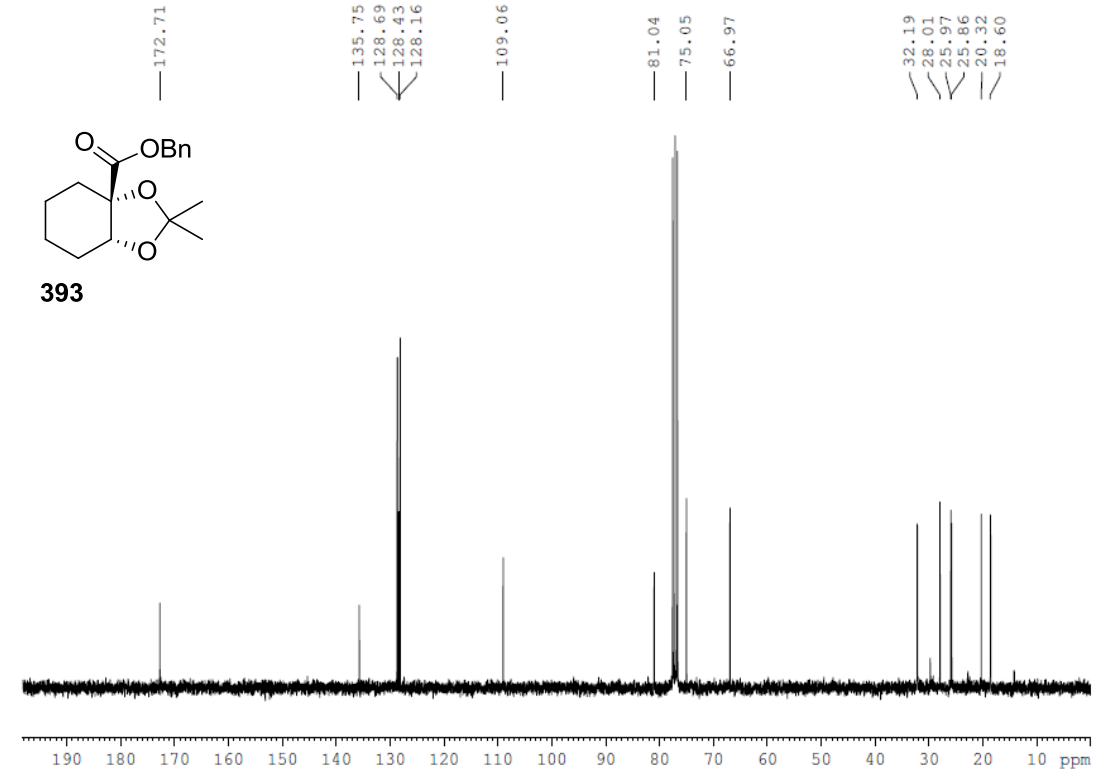
NOESY

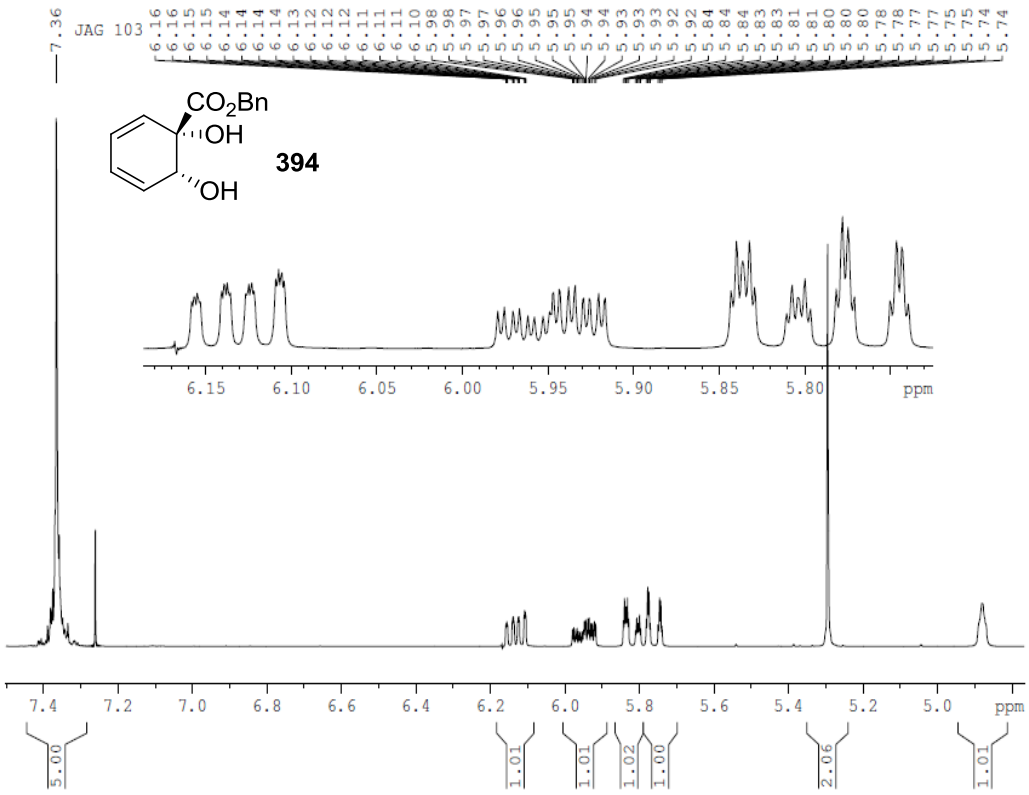

JAG 403 A NOESY
ppm
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 ppm

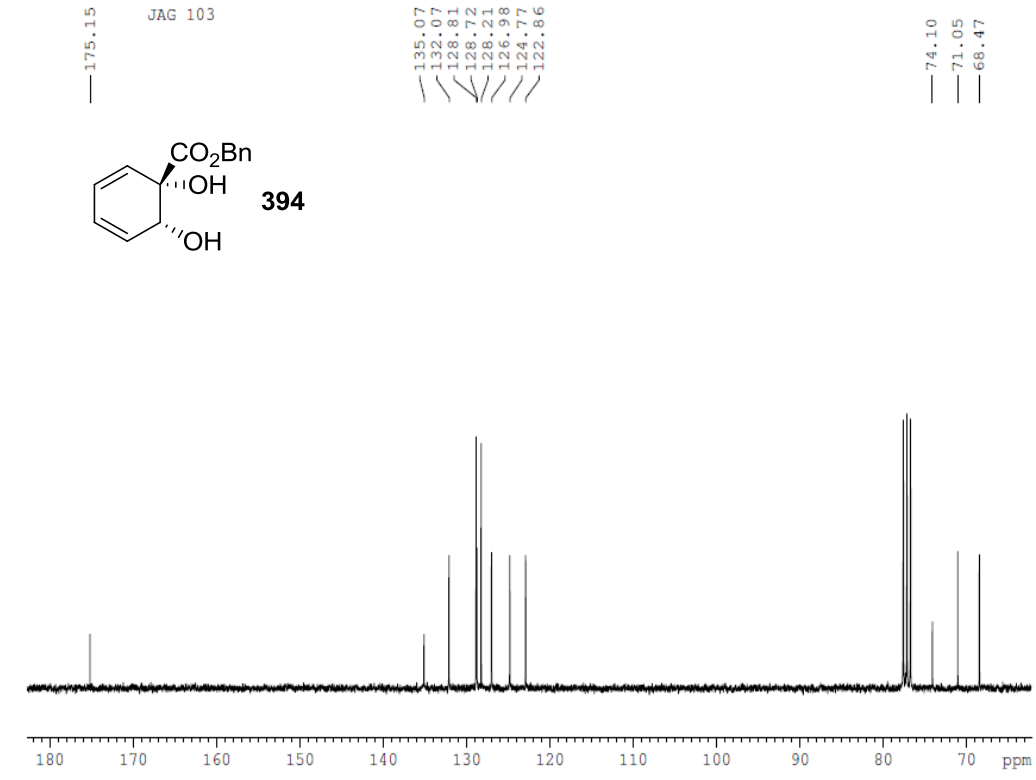

JAG 343 A
7.358
5.243
5.238
3.894
3.876
3.849
3.830
1.884
1.208
O
OBn
OH
OH
392
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
5.01
2.00
1.00
9.16

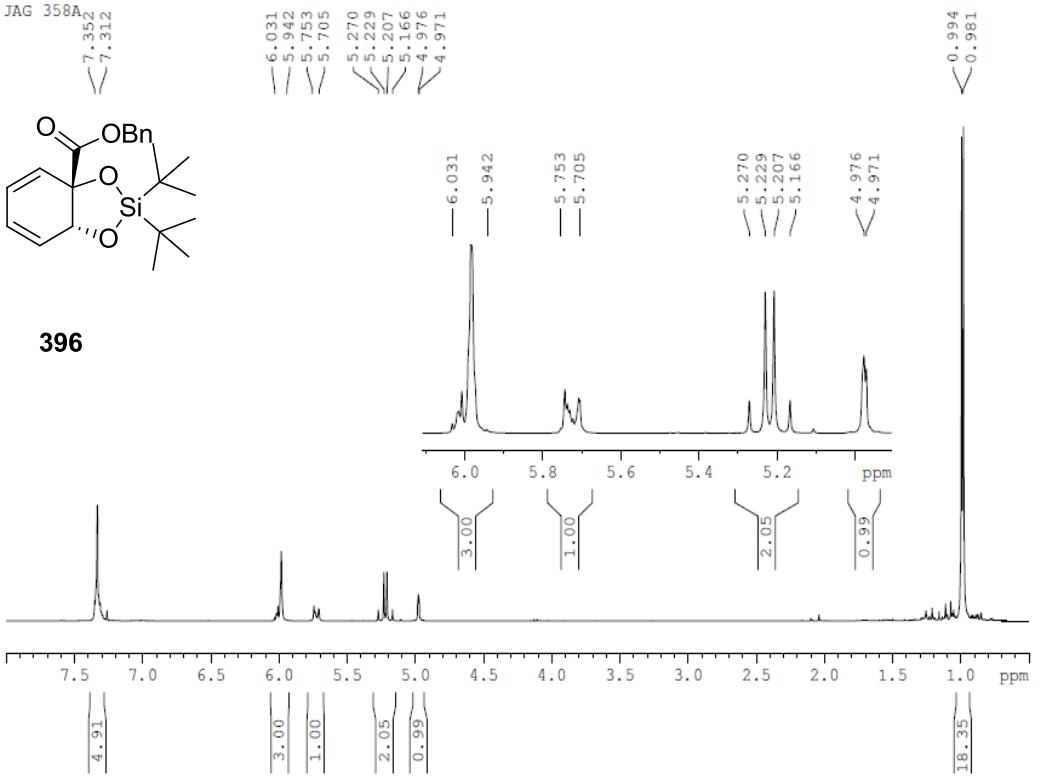

JAG 343 A
176.07
135.26
128.59
128.39
127.93
76.81
72.22
67.61
34.24
30.21
23.97
19.79
O
OBn
OH
OH
392
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

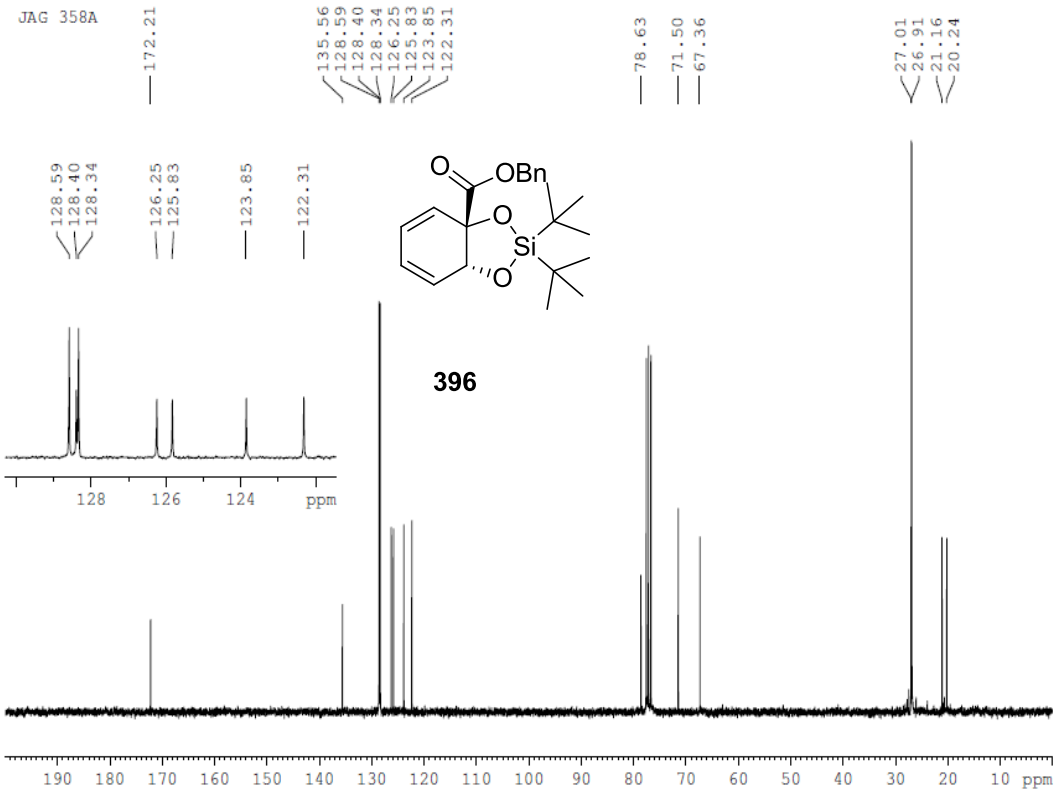

7.367
7.350
7.332
5.215
4.399
4.388
4.376
2.050
1.974
1.829
1.252
OBn
O
O
O
393
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
5.06
2.06
1.00
2.15
12.26

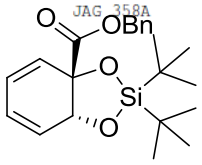

172.71
135.75
128.69
128.43
128.16
109.06
81.04
75.05
66.97
32.19
28.01
25.97
25.86
20.32
18.60
OBn
O
O
O
393
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


JAG 103
CO2Bn
OH
OH
394
ppm
5.00
1.01
1.01
1.02
1.00
2.06
1.01


JAG 103
CO2Bn
OH
OH
394
ppm

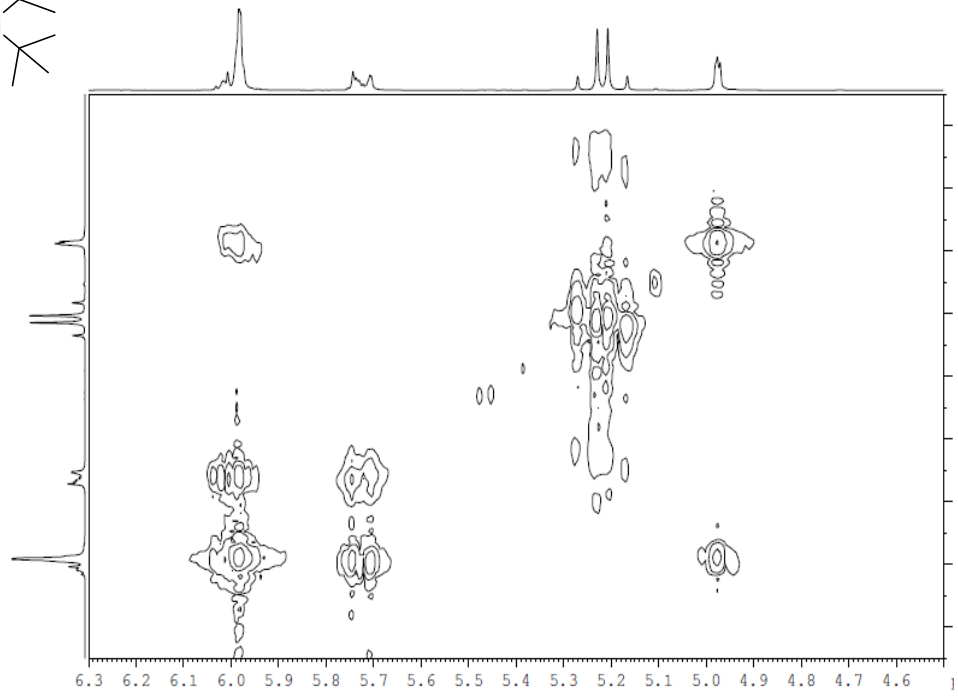

JAG 358A
7.352
7.312
6.031
5.942
5.753
5.705
5.270
5.229
5.207
5.166
4.976
4.971
0.994
0.981
OBn
O
O
Si
O
396
ppm
4.91
3.00
1.00
2.05
0.99
18.35

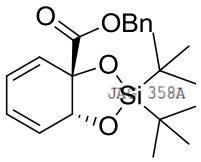

JAG 358A
172.21
135.56
128.59
128.40
128.34
126.25
125.83
123.85
122.31
78.63
71.50
67.36
27.01
26.91
21.16
20.24
OBn
O
O
Si
O
396
ppm



COSY

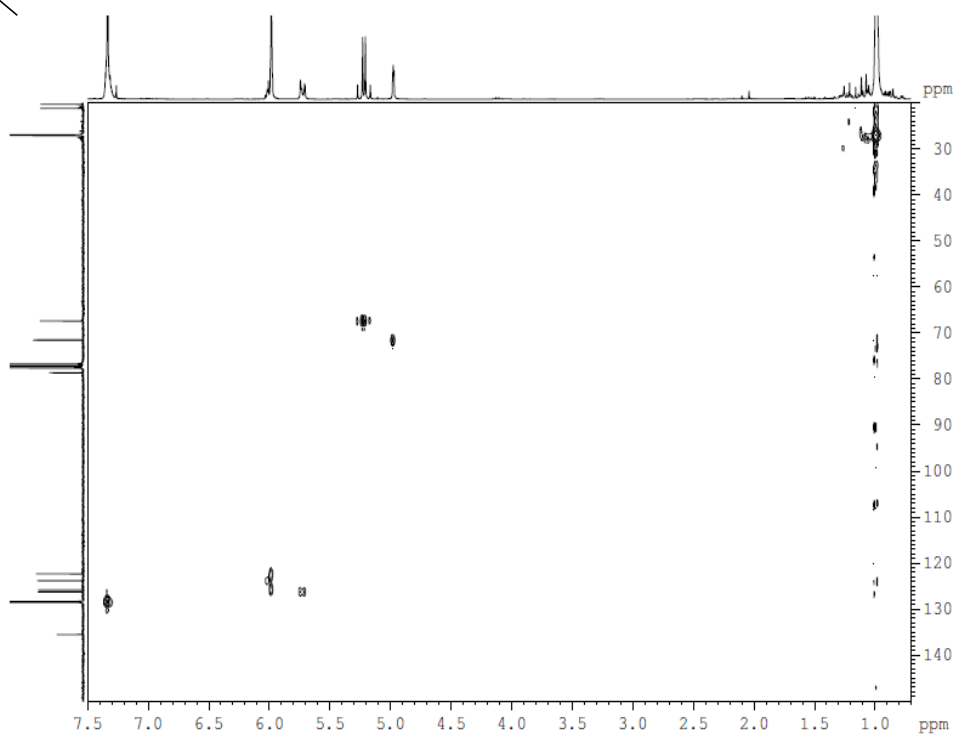
396

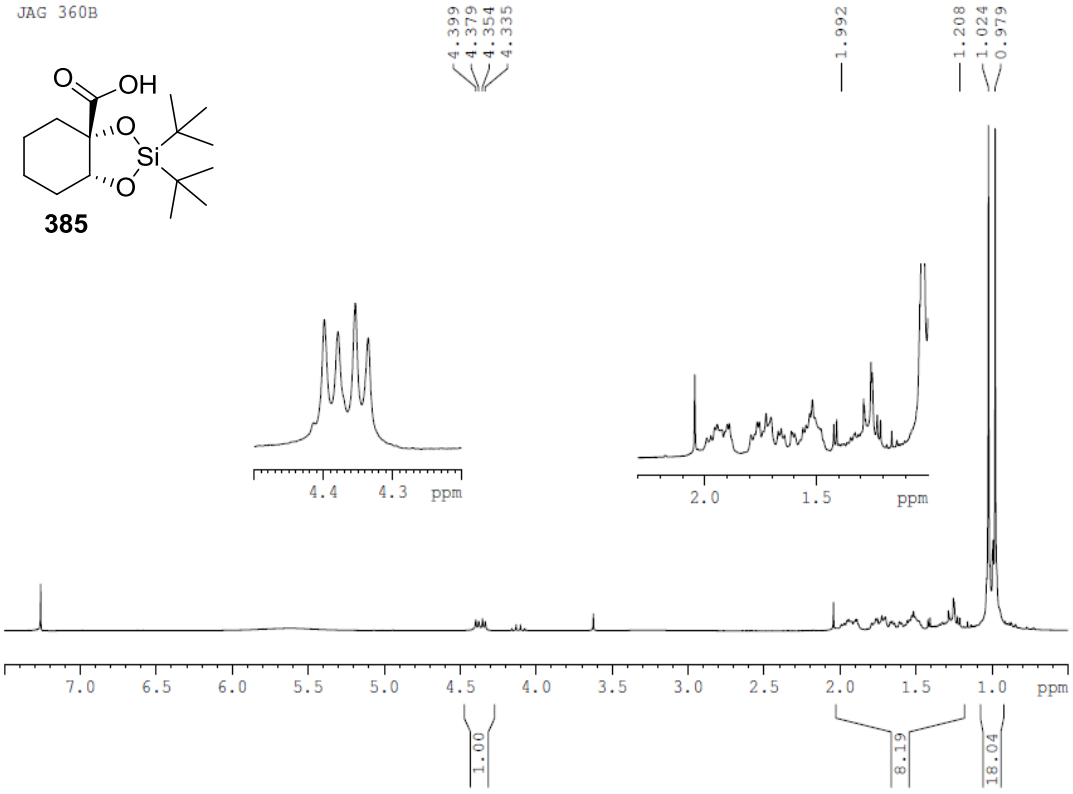


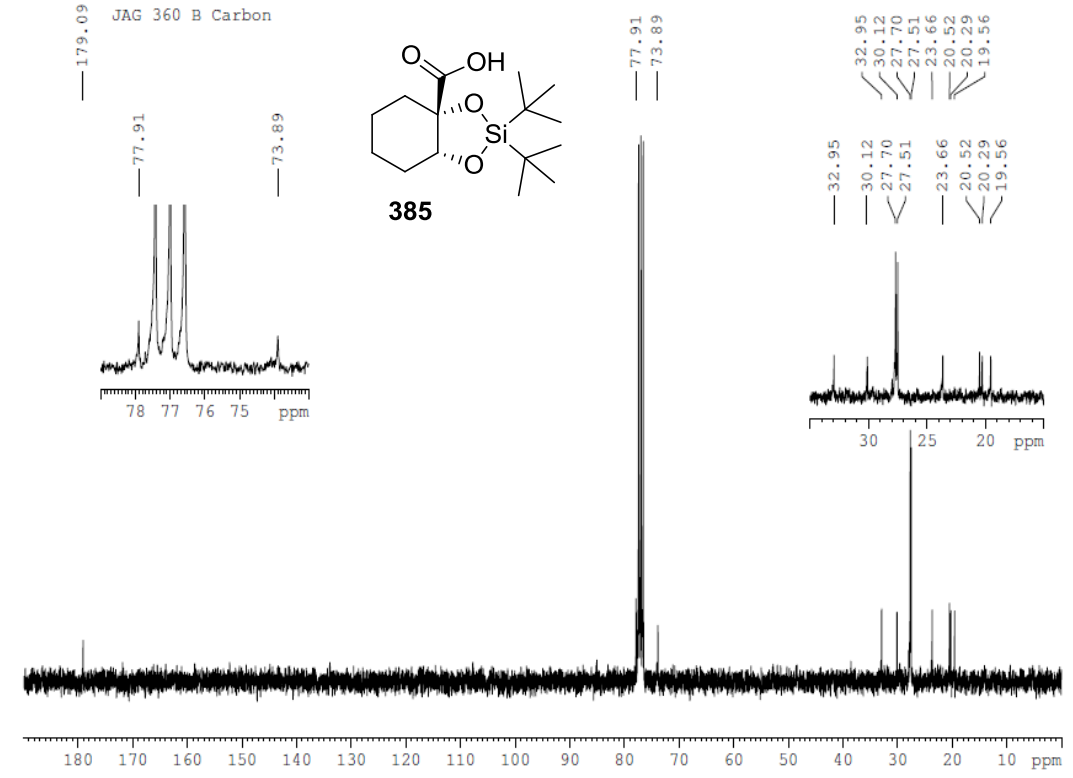


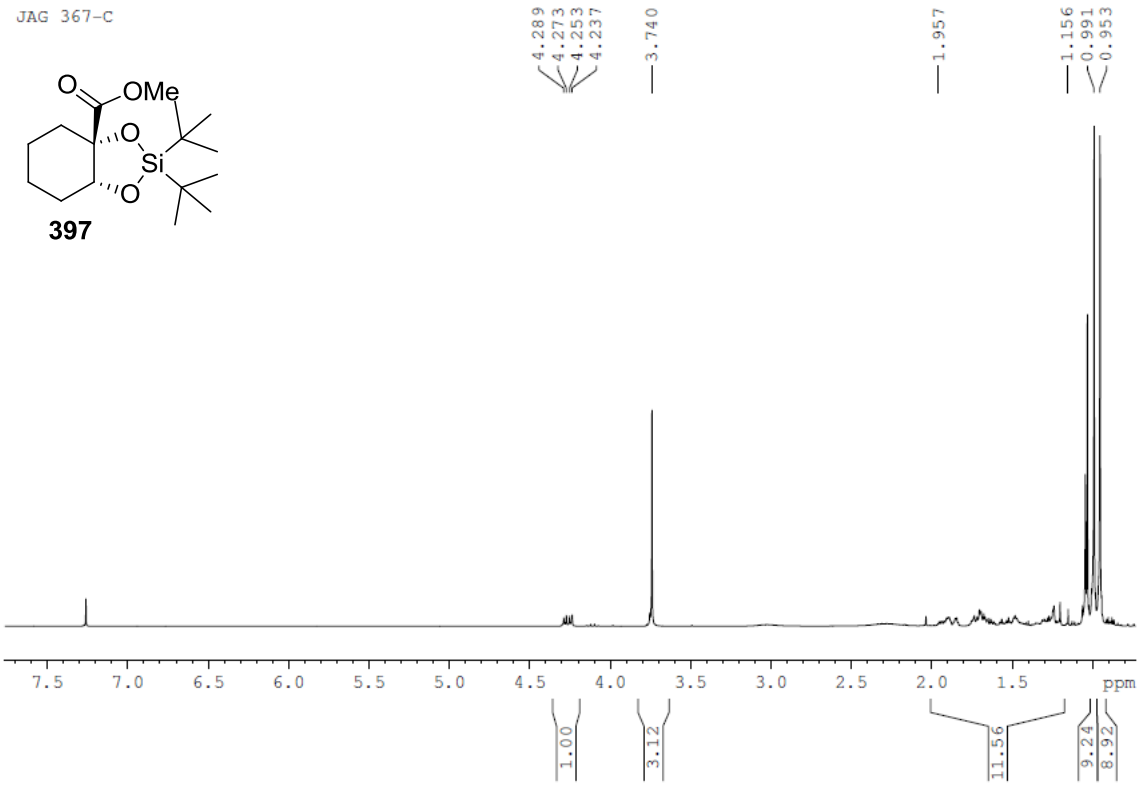
HSQC

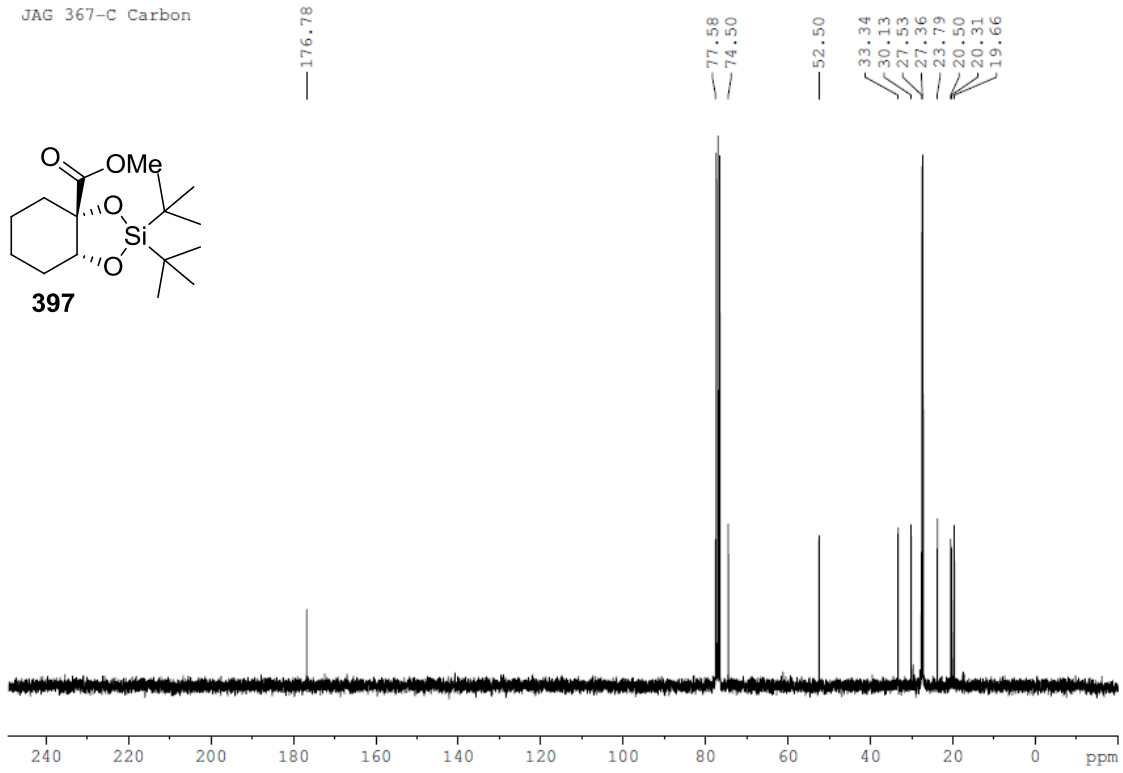
396

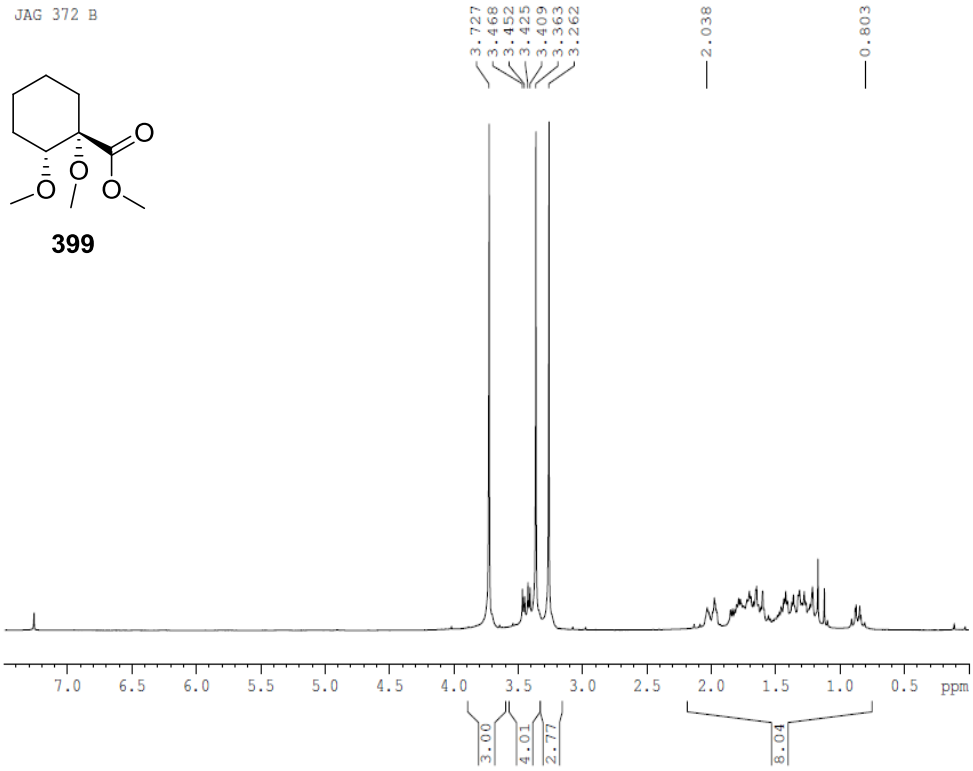



JAG 360B
4.399
4.379
4.354
4.335
1.992
1.208
1.024
0.979
385
4.4
4.3
ppm
2.0
1.5
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
8.19
18.04

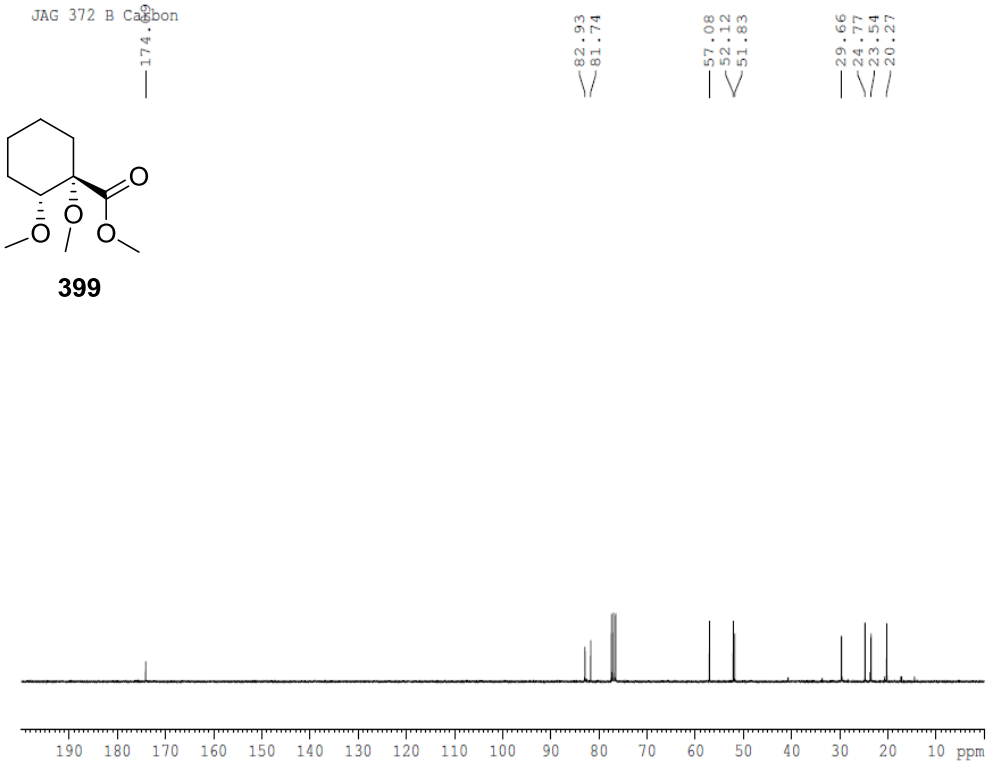

JAG 360 B Carbon
179.09
77.91
73.89
385
77.91
73.89
78
77
76
75
ppm
32.95
30.12
27.70
27.51
23.66
20.52
20.29
19.56
30
25
20
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


JAG 367-C
4.289
4.273
4.253
4.237
3.740
1.957
1.156
0.991
0.953
OMe
O
O
Si
O
397
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
3.12
11.56
9.24
8.92

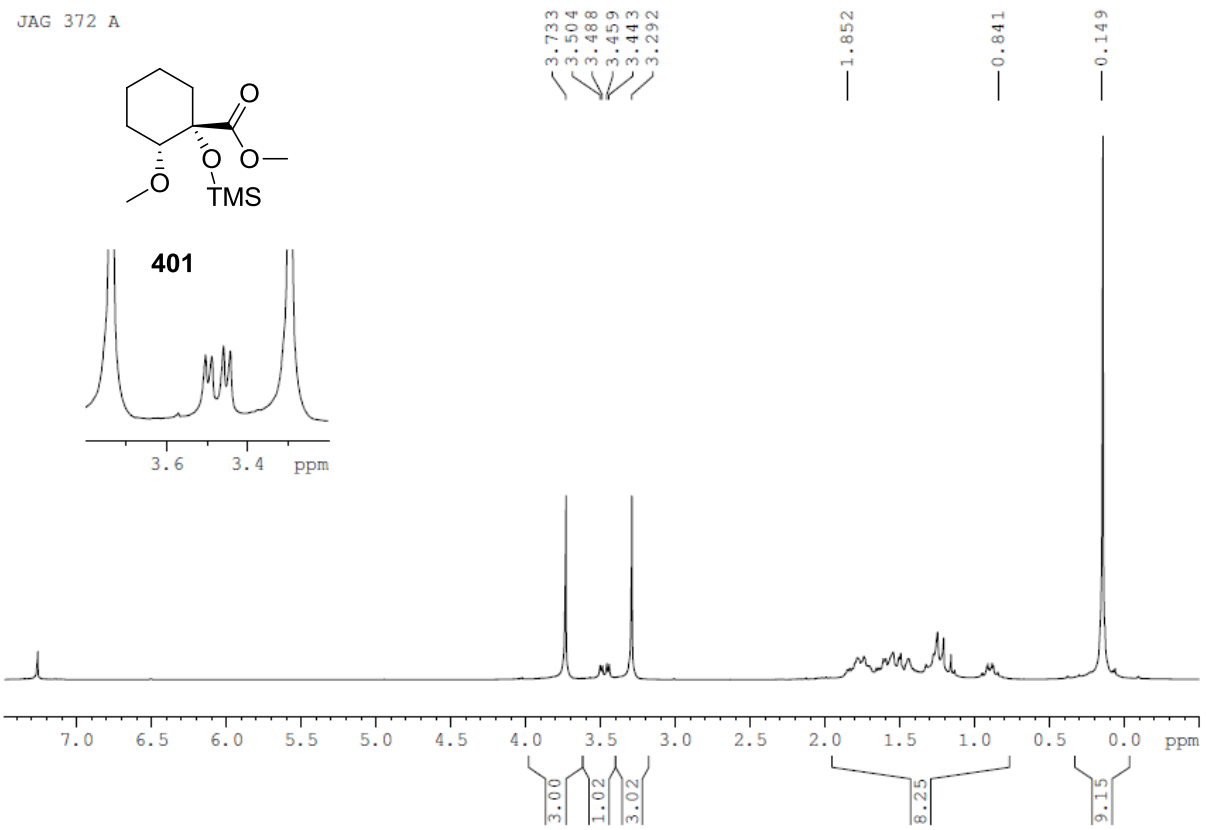

JAG 367-C Carbon
176.78
77.58
74.50
52.50
33.34
30.13
27.53
27.36
23.79
20.50
20.31
19.66
OMe
O
O
Si
O
397
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

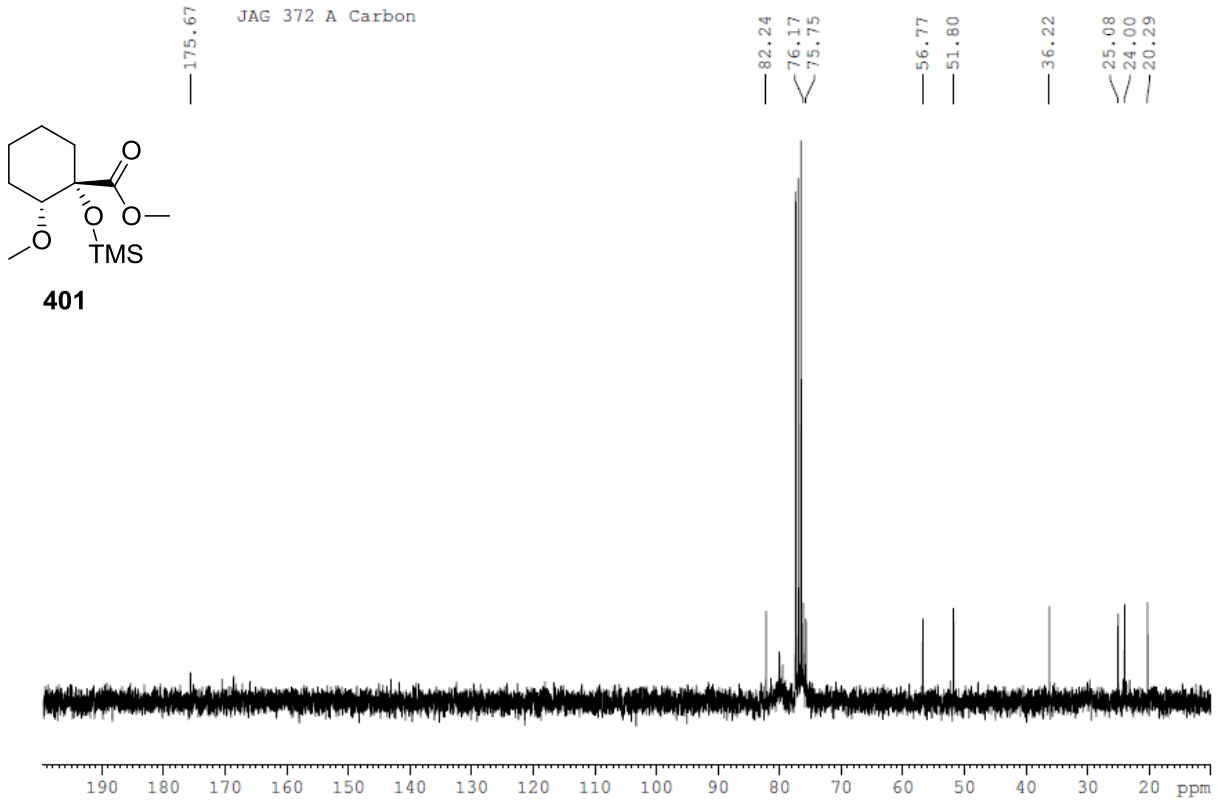

JAG 372 B
3.727
3.468
3.452
3.425
3.409
3.363
3.262
2.038
0.803
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.00
4.01
2.77
8.04

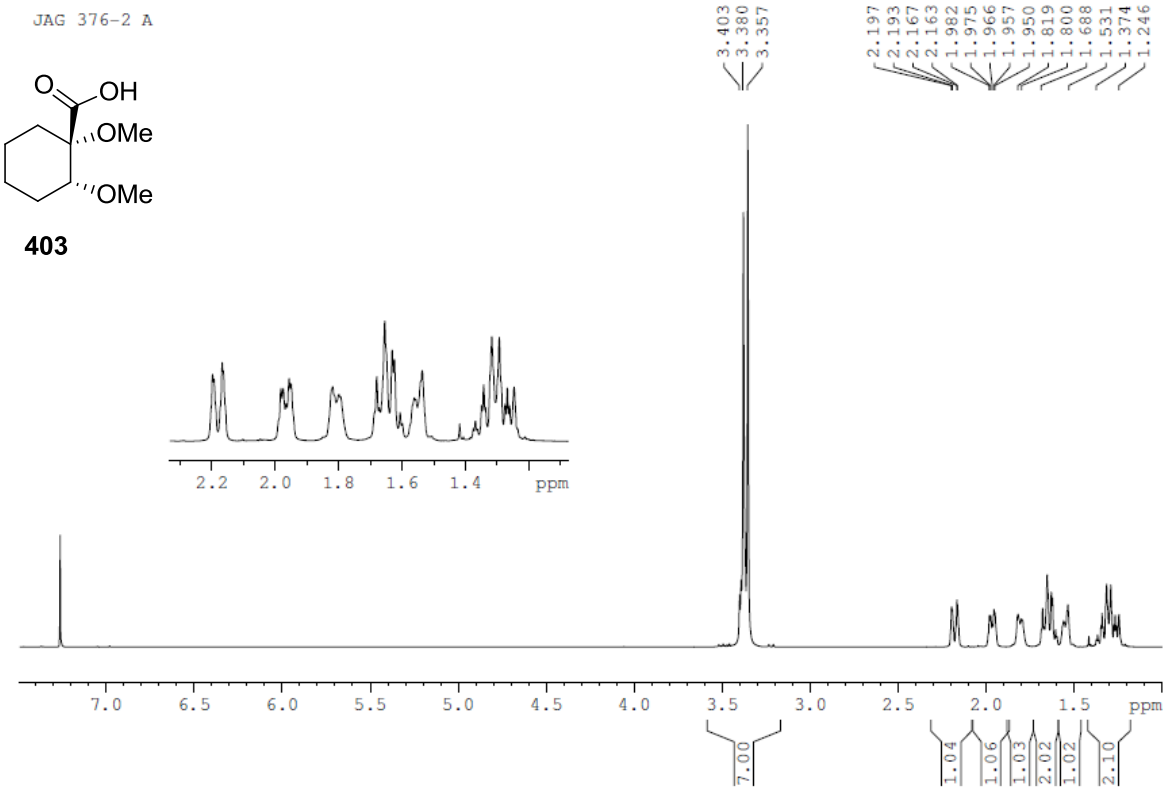
399

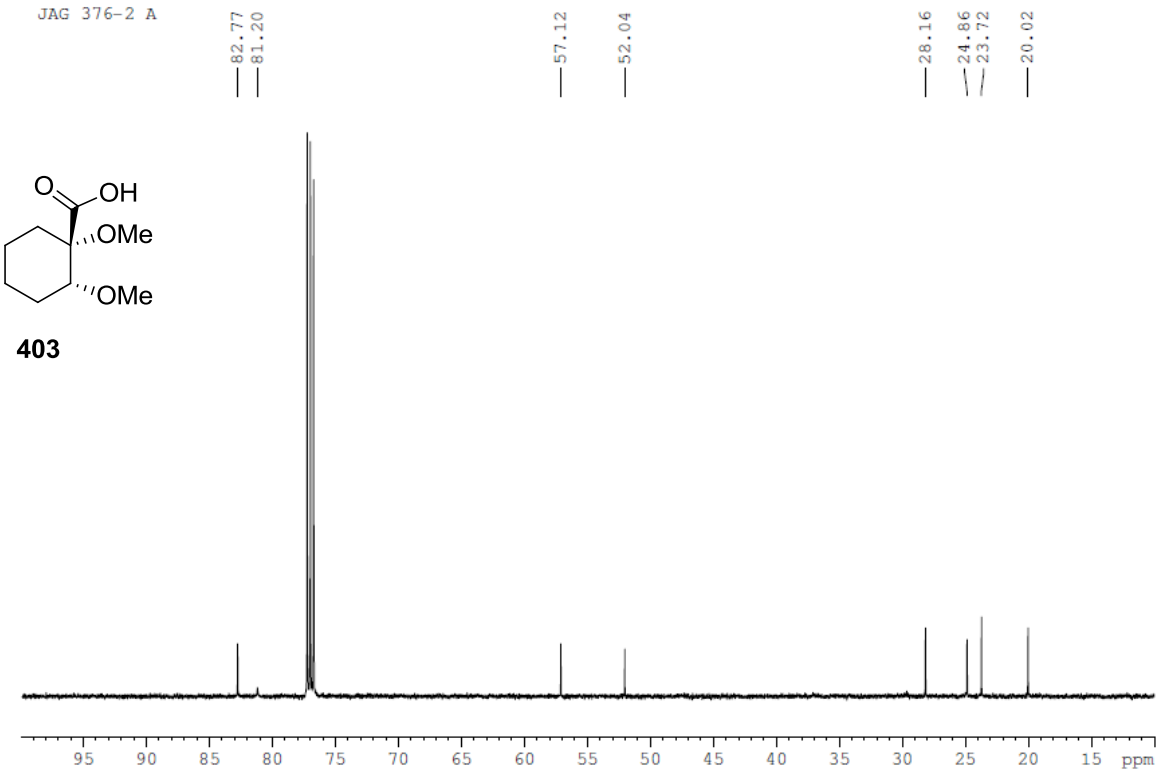

JAG 372 B Carbon
174.69
82.93
81.74
57.08
52.12
51.83
29.66
24.77
23.54
20.27
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

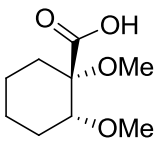
399


JAG 372 A
3.733
3.504
3.488
3.459
3.443
3.292
1.852
0.841
0.149
O
O
O
O
TMS
401
3.6
3.4
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.00
1.02
3.02
8.25
9.15


JAG 372 A Carbon
175.67
82.24
76.17
75.75
56.77
51.80
36.22
25.08
24.00
20.29
O
O
O
O
TMS
401
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

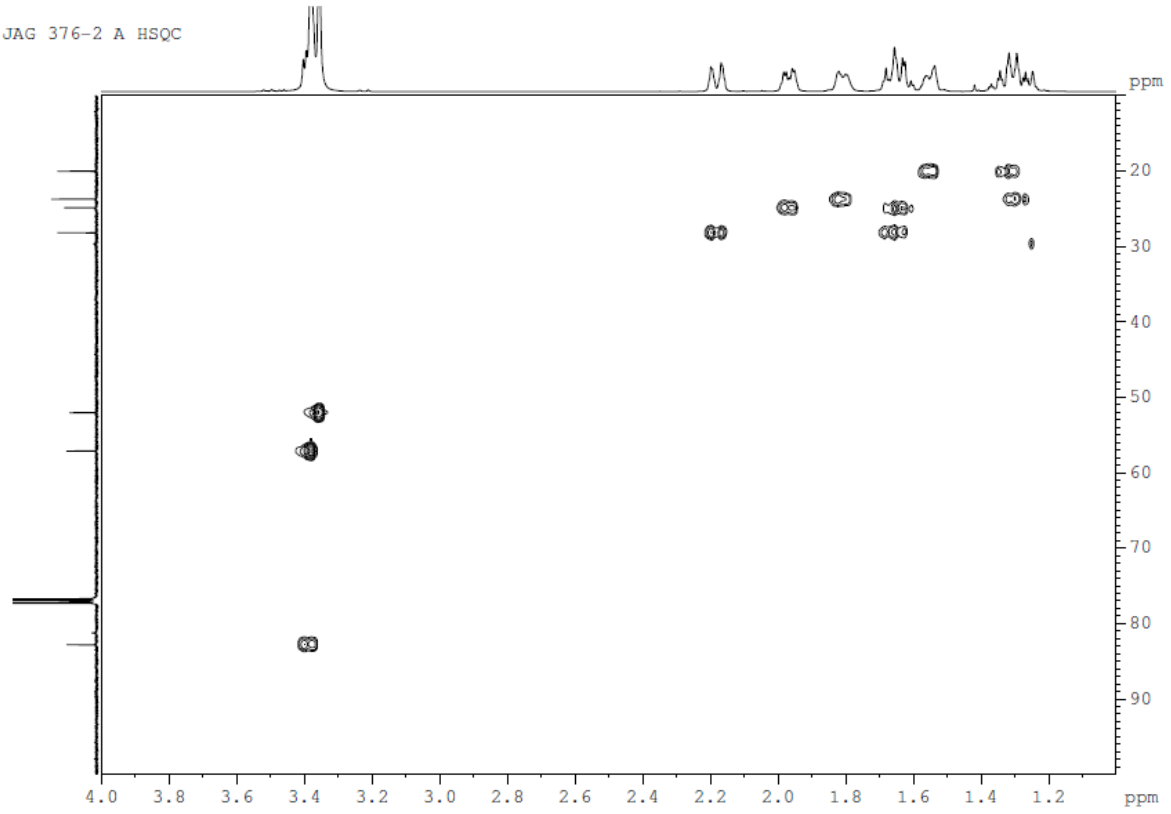

JAG 376-2 A
OH
OMe
OMe
403
3.403
3.380
3.357
2.197
2.193
2.167
2.163
1.982
1.975
1.966
1.957
1.950
1.819
1.800
1.688
1.531
1.374
1.246
2.2
2.0
1.8
1.6
1.4
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
7.00
1.04
1.06
1.03
2.02
1.02
2.10

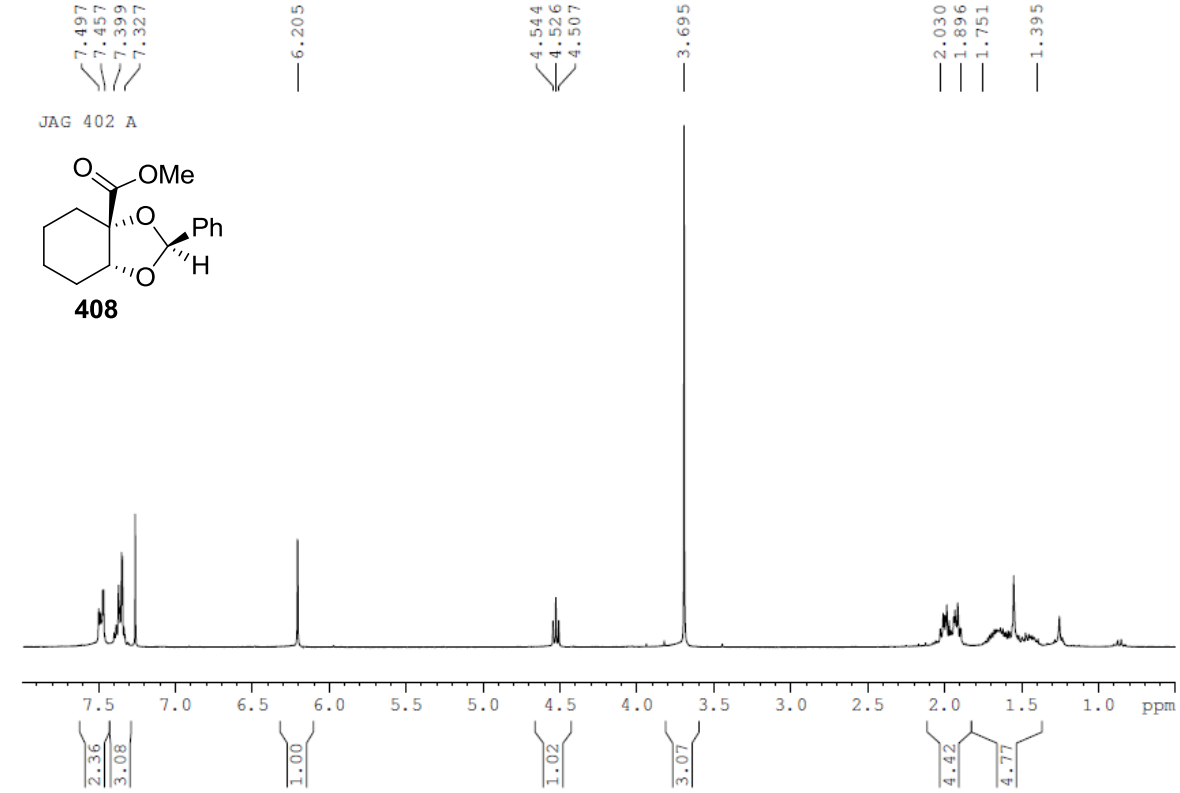

JAG 376-2 A
82.77
81.20
57.12
52.04
28.16
24.86
23.72
20.02
OH
OMe
OMe
403
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
ppm

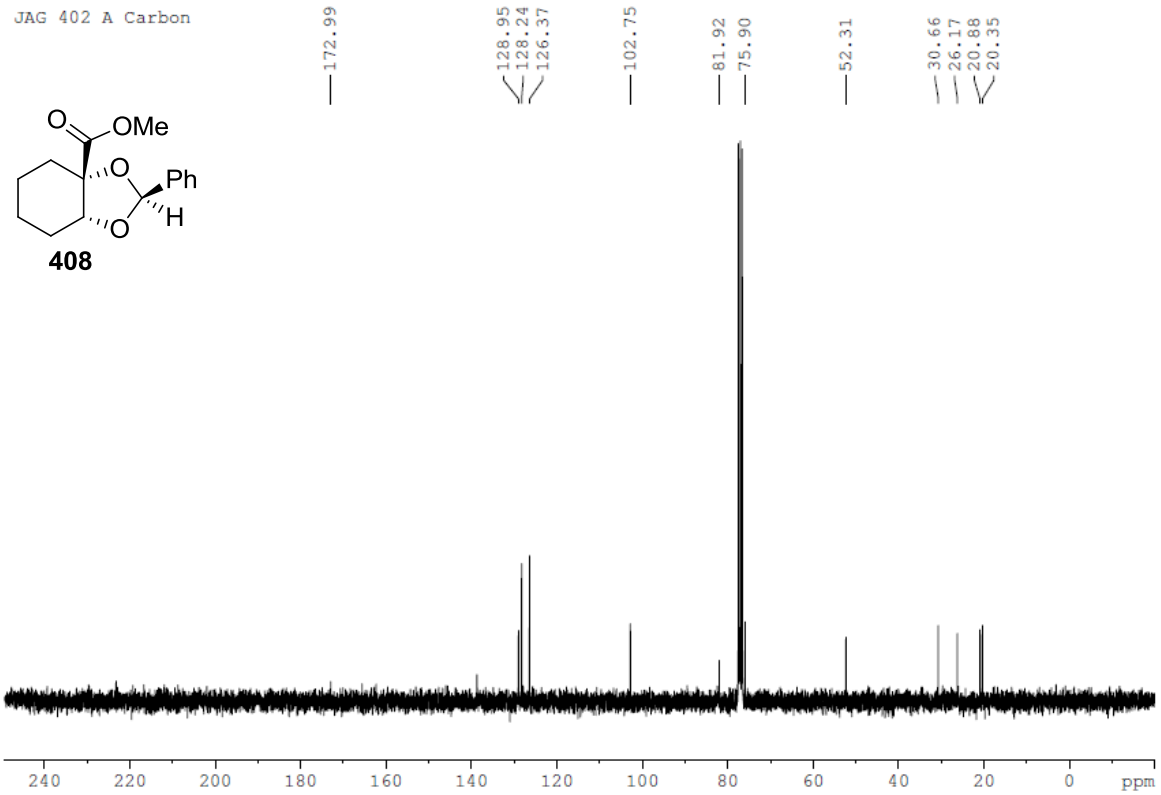

O
OH
OMe
OMe

HSQC

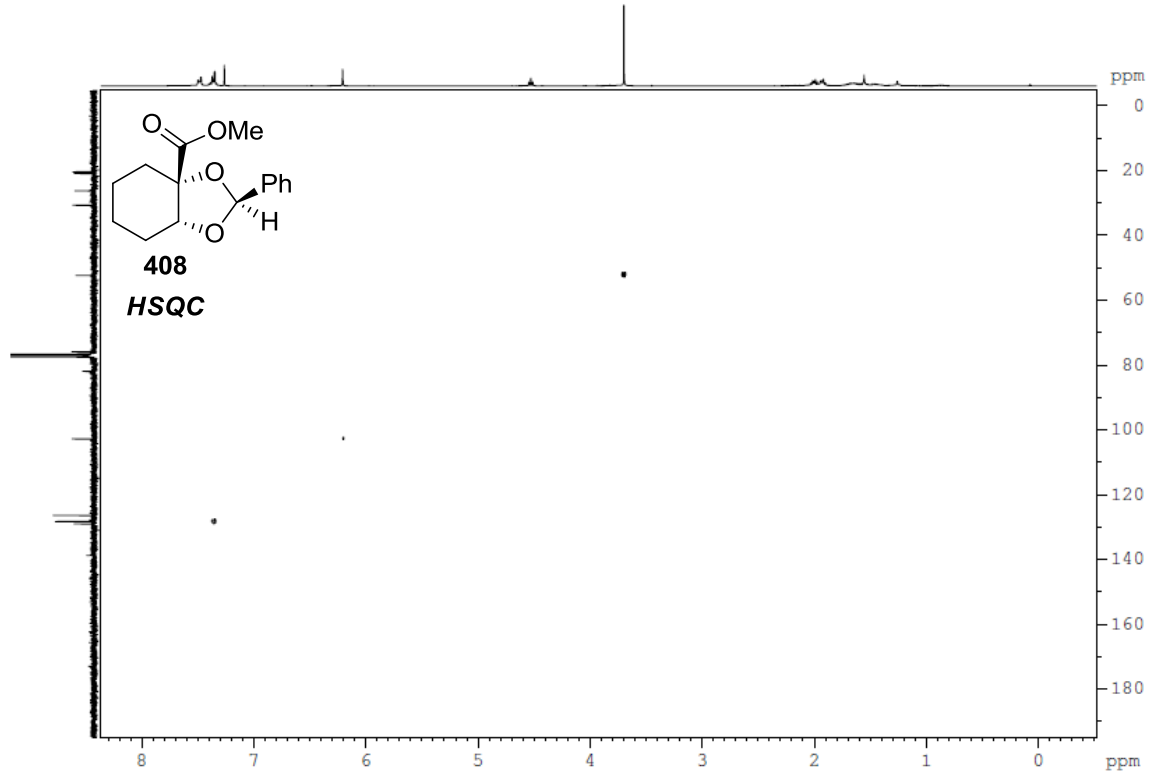
403


JAG 376-2 A HSQC
ppm
20
30
40
50
60
70
80
90
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
ppm

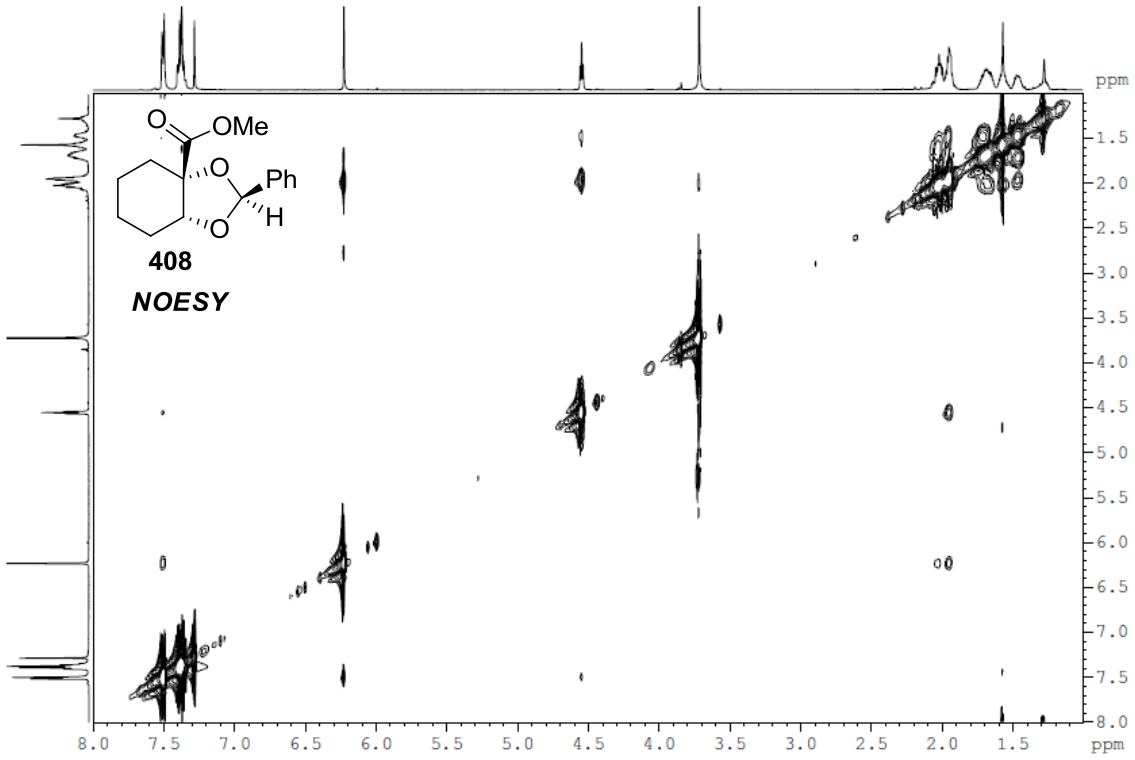

7.497
7.457
7.399
7.327
6.205
4.544
4.526
4.507
3.695
2.030
1.896
1.751
1.395
JAG 402 A
O
OMe
O
Ph
H
O
408
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.36
3.08
1.00
1.02
3.07
4.42
4.77

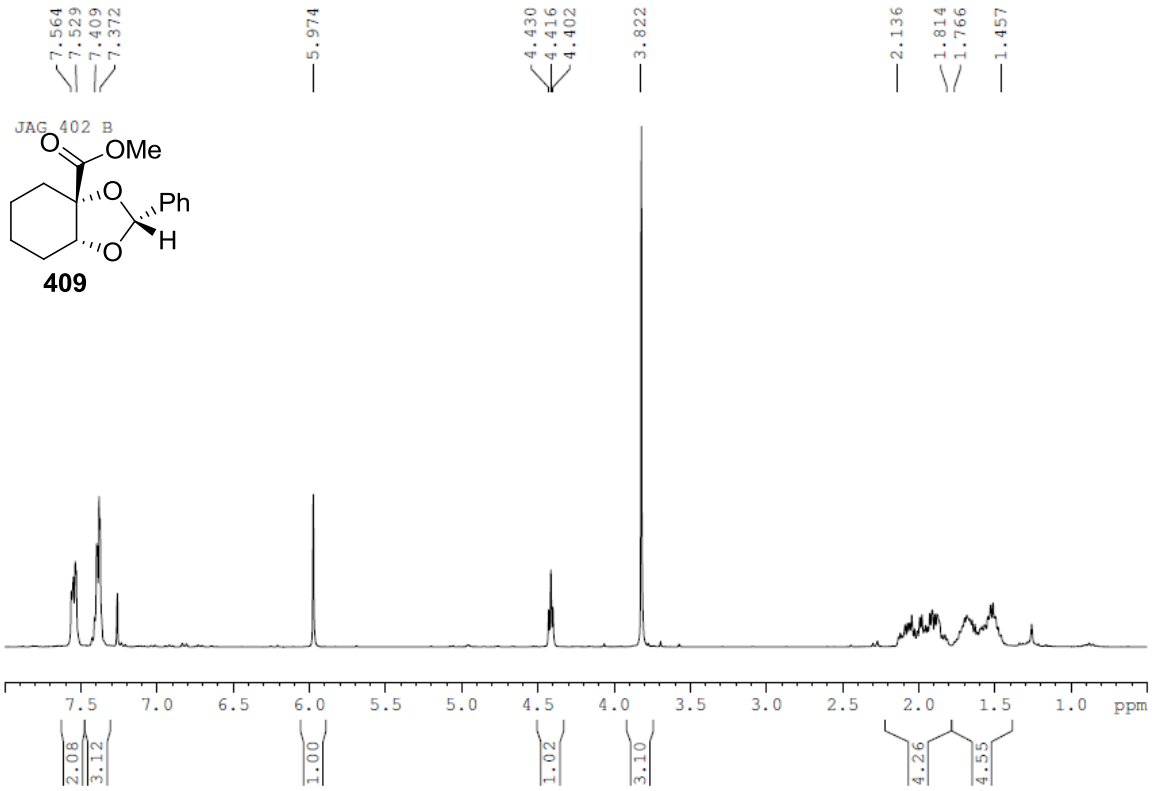

JAG 402 A Carbon
172.99
128.95
128.24
126.37
102.75
81.92
75.90
52.31
30.66
26.17
20.88
20.35
O
OMe
O
Ph
H
O
408
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

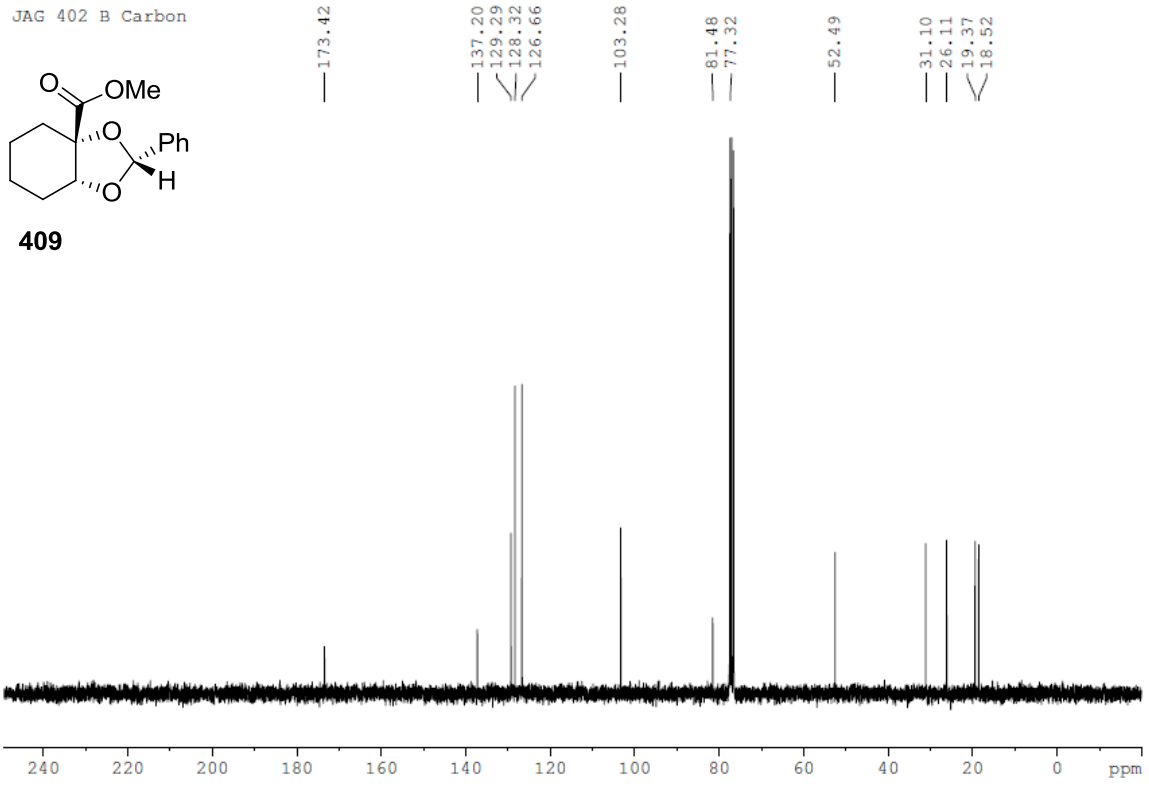
JAG 402 A HMQC



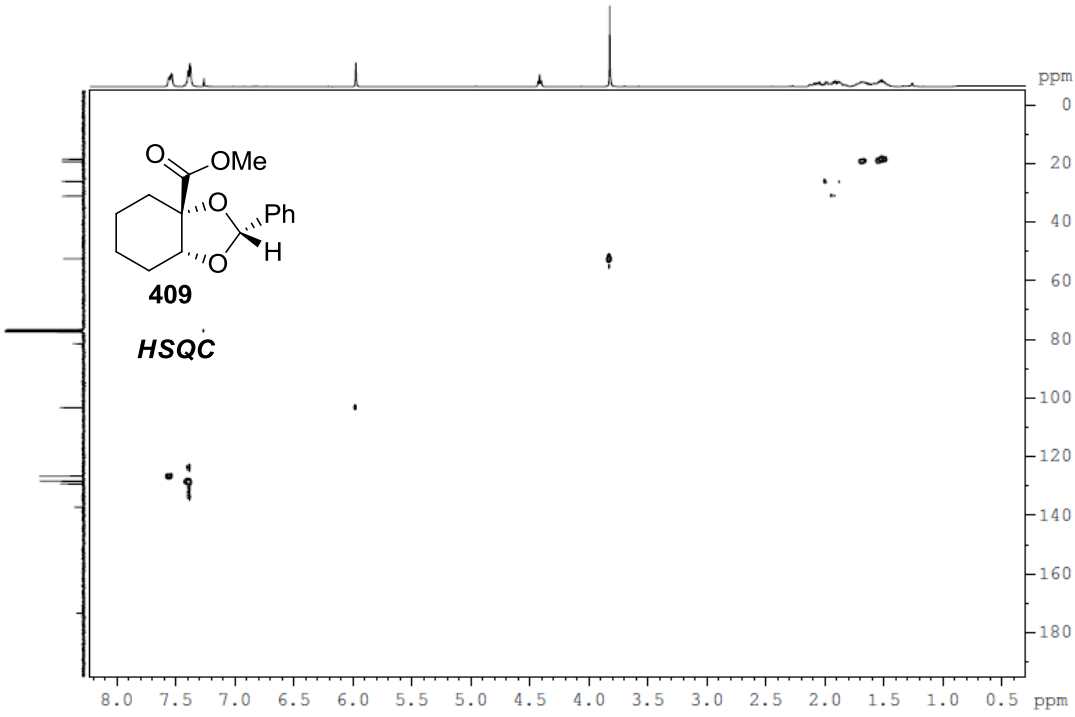
JAG 402 A

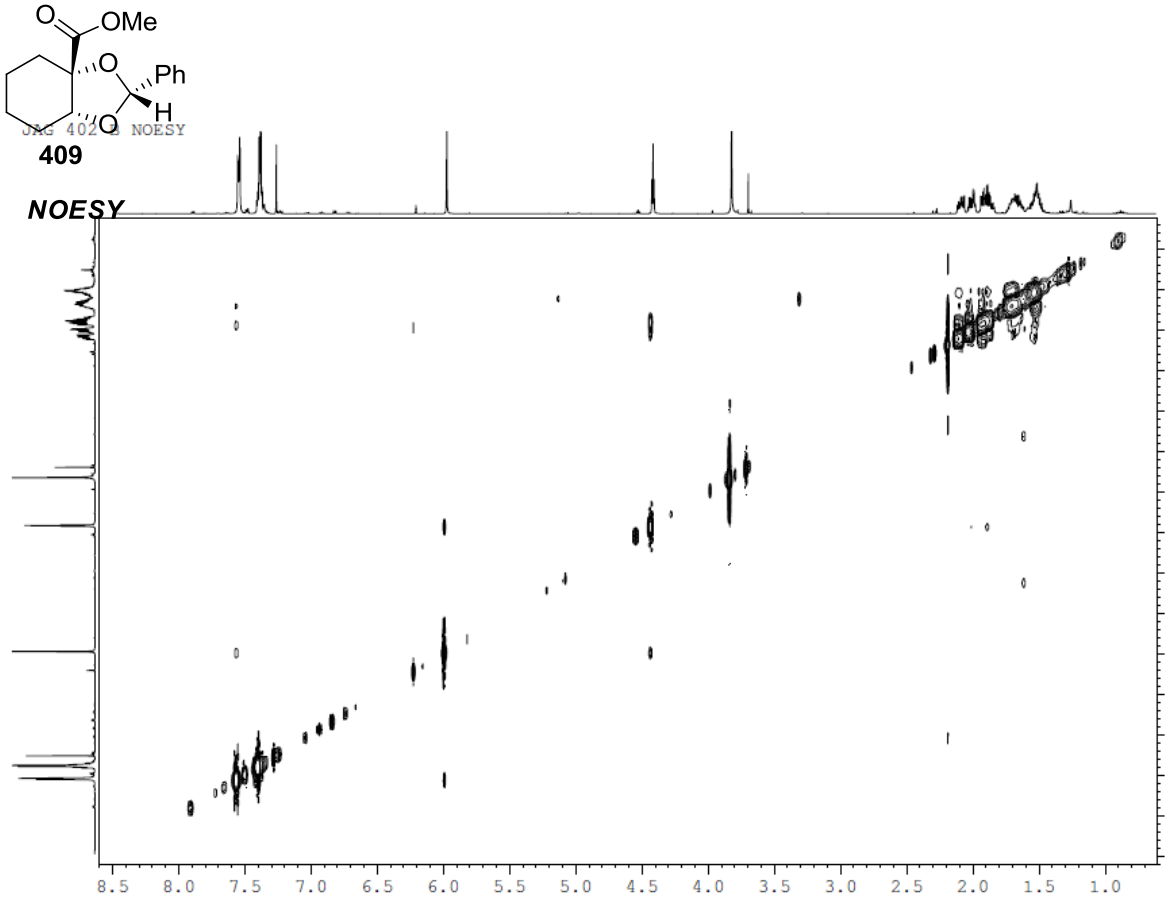


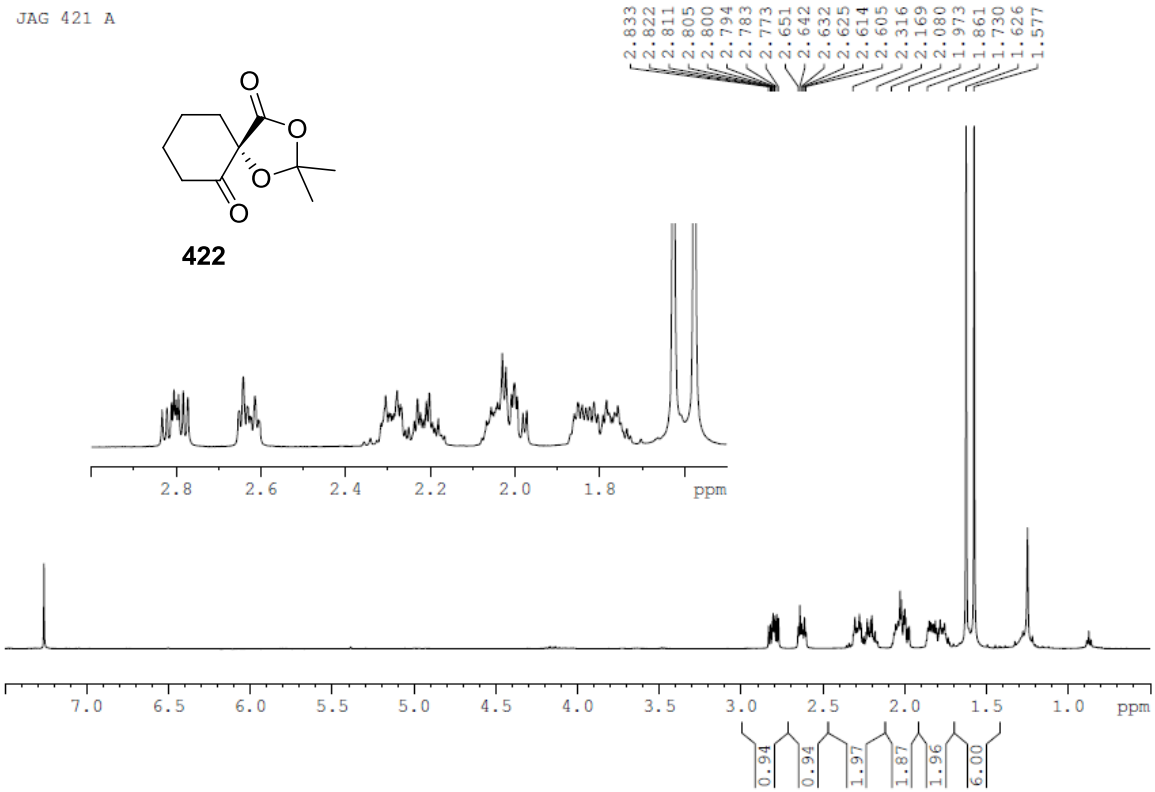

7.564
7.529
7.409
7.372
5.974
4.430
4.416
4.402
3.822
2.136
1.814
1.766
1.457
JAG 402 B
OMe
Ph
H
409
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.08
3.12
1.00
1.02
3.10
4.26
4.55

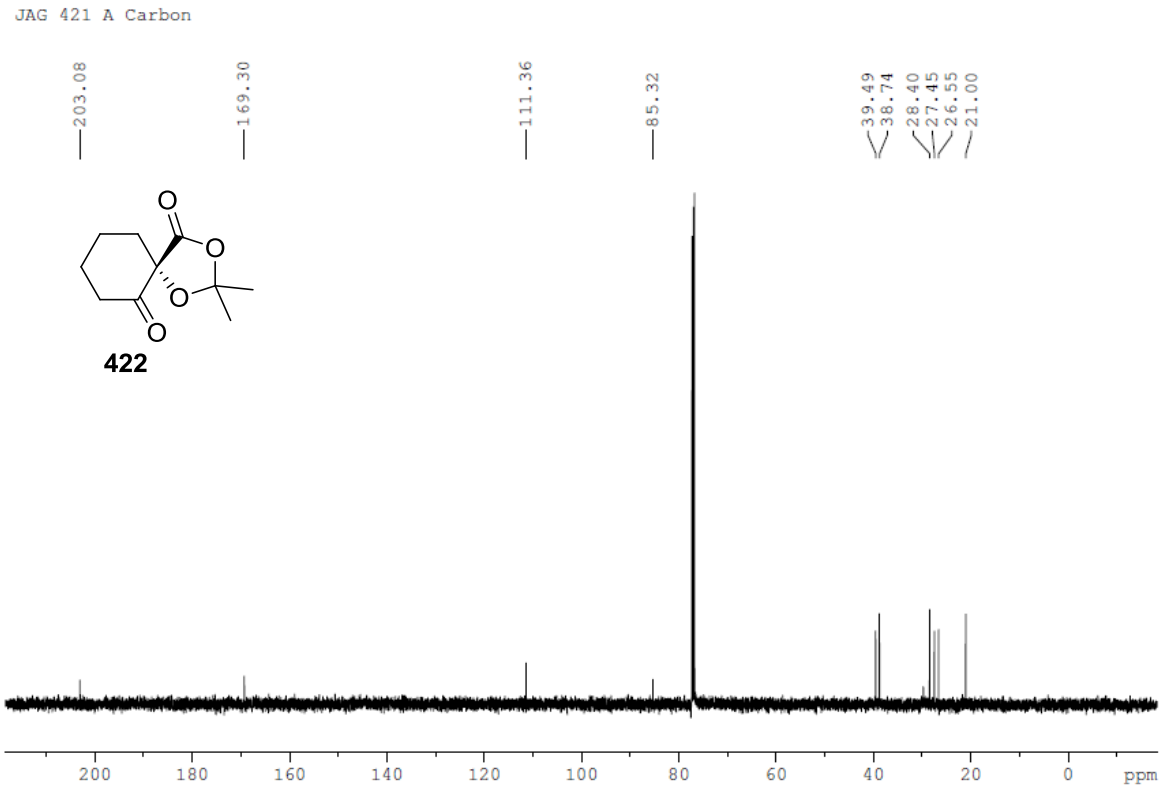

JAG 402 B Carbon
173.42
137.20
129.29
128.32
126.66
103.28
81.48
77.32
52.49
31.10
26.11
19.37
18.52
OMe
Ph
H
409
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

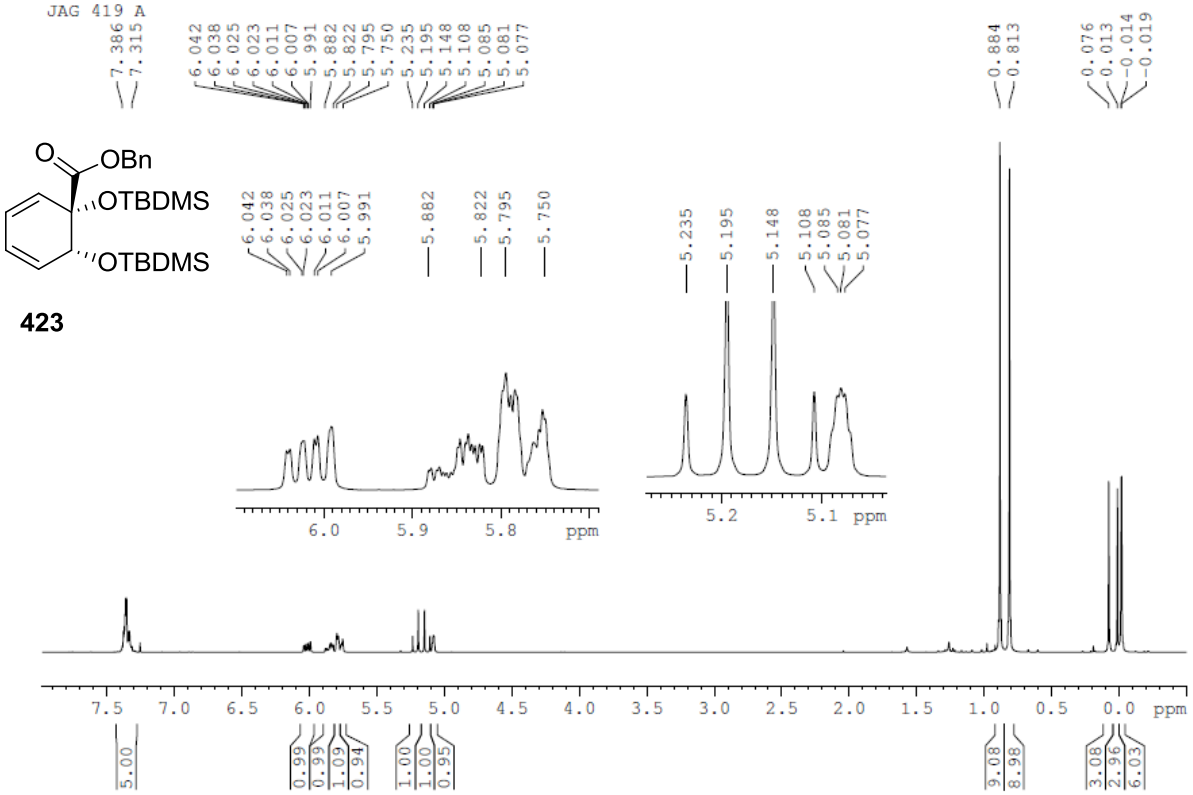
JAG 402 B HSQC

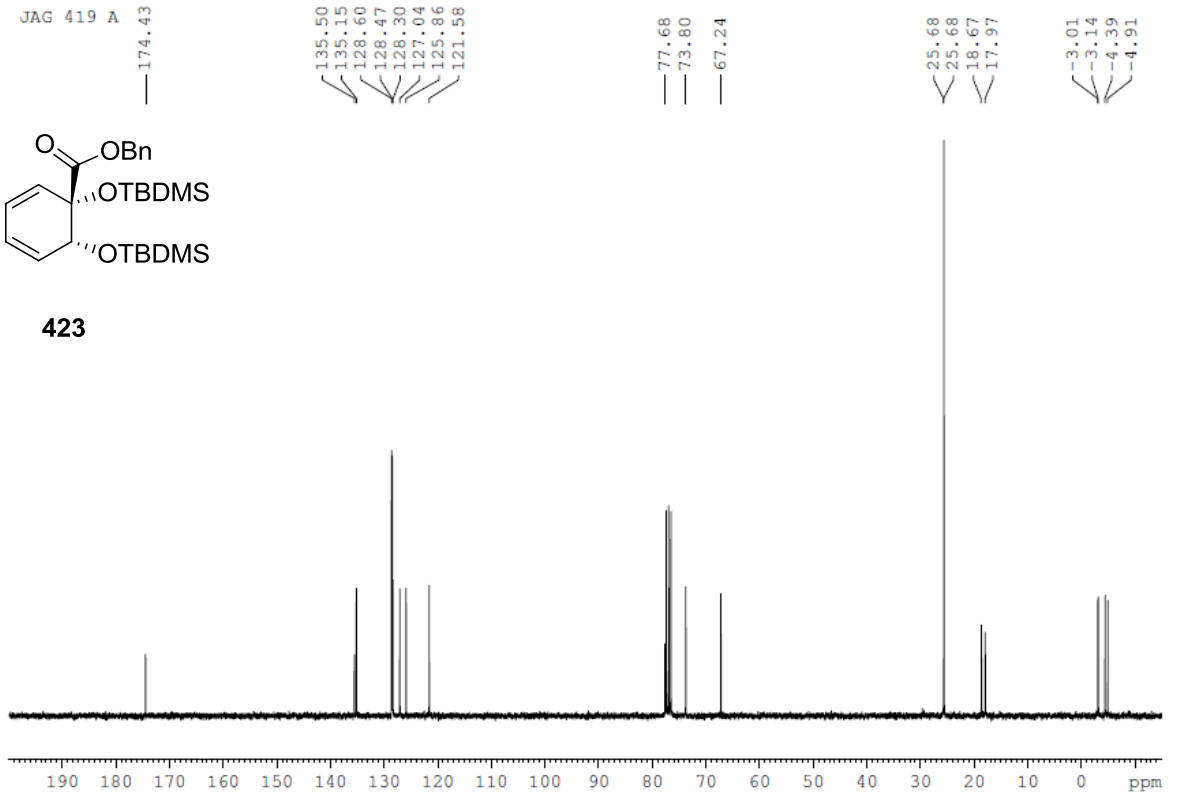


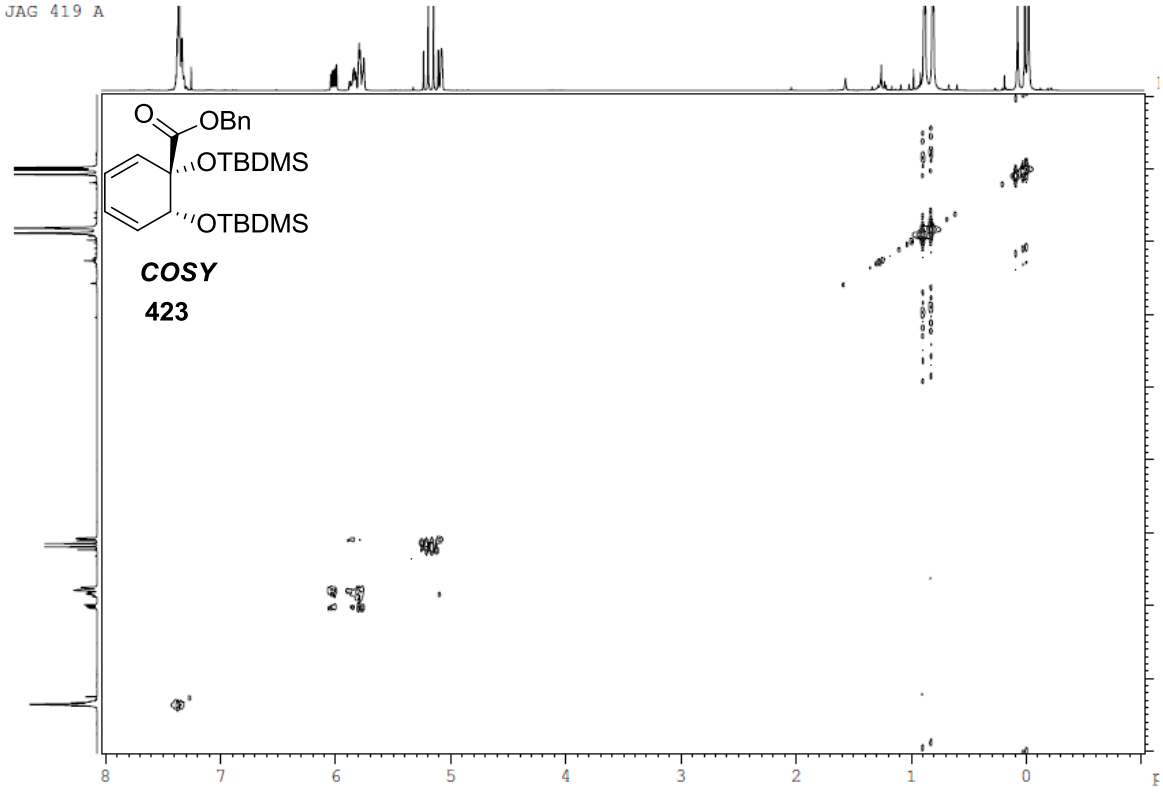


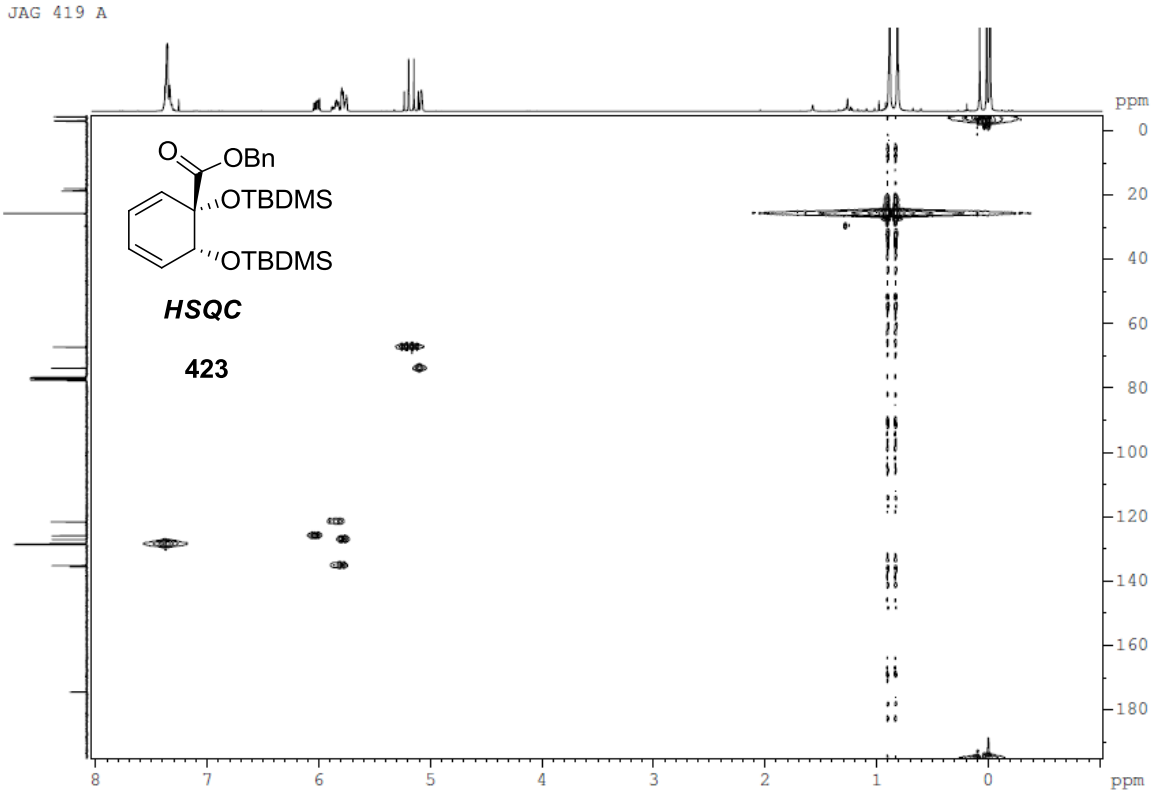

JAG 421 A
2.833
2.822
2.811
2.805
2.800
2.794
2.783
2.773
2.651
2.642
2.632
2.625
2.614
2.605
2.316
2.169
2.080
1.973
1.861
1.730
1.626
1.577
422
2.8
2.6
2.4
2.2
2.0
1.8
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.94
0.94
1.97
1.87
1.96
6.00

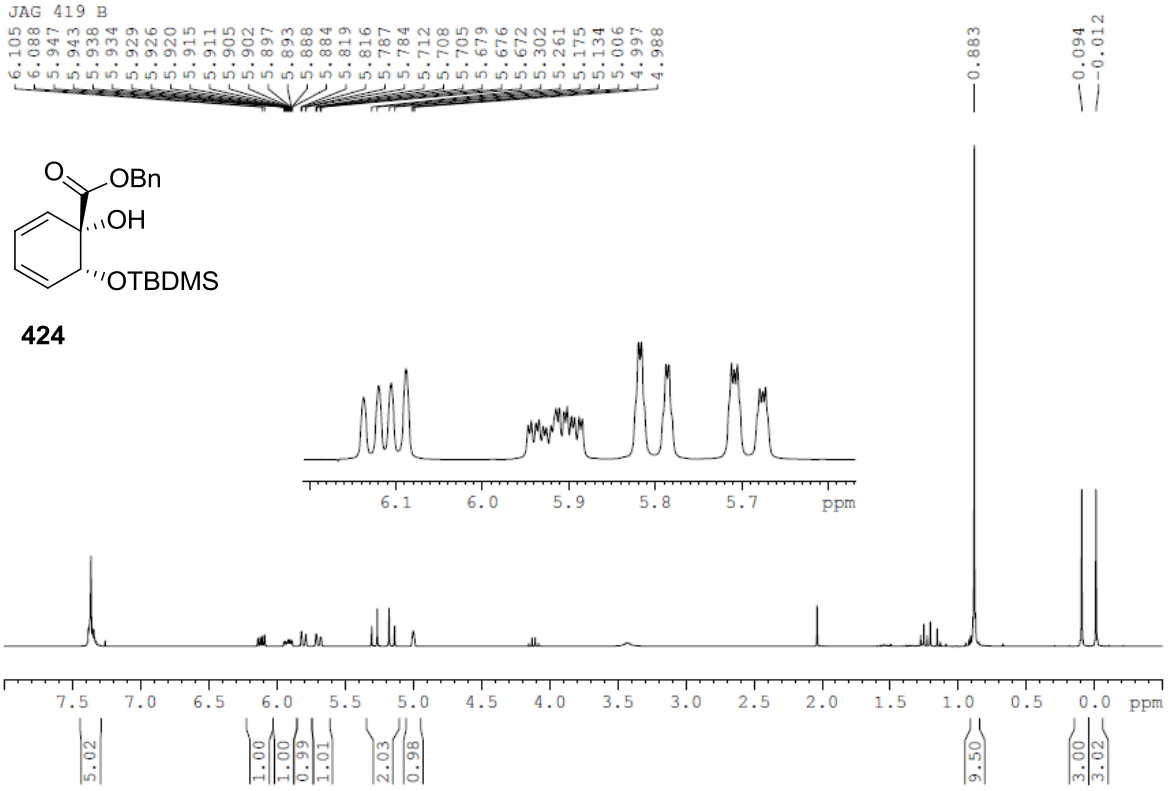

JAG 421 A Carbon
203.08
169.30
111.36
85.32
39.49
38.74
28.40
27.45
26.55
21.00
422
200
180
160
140
120
100
80
60
40
20
0
ppm


JAG 419 A
7.386
7.315
6.042
6.038
6.025
6.023
6.011
6.007
5.991
5.882
5.822
5.795
5.750
5.235
5.195
5.148
5.108
5.085
5.081
5.077
0.884
0.813
0.076
0.013
-0.014
-0.019
O
OBn
OTBDMS
OTBDMS
423
6.0
5.9
5.8
ppm
5.2
5.1
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
5.00
0.99
0.99
1.09
0.94
1.00
1.00
0.95
9.08
8.98
3.08
2.96
6.03

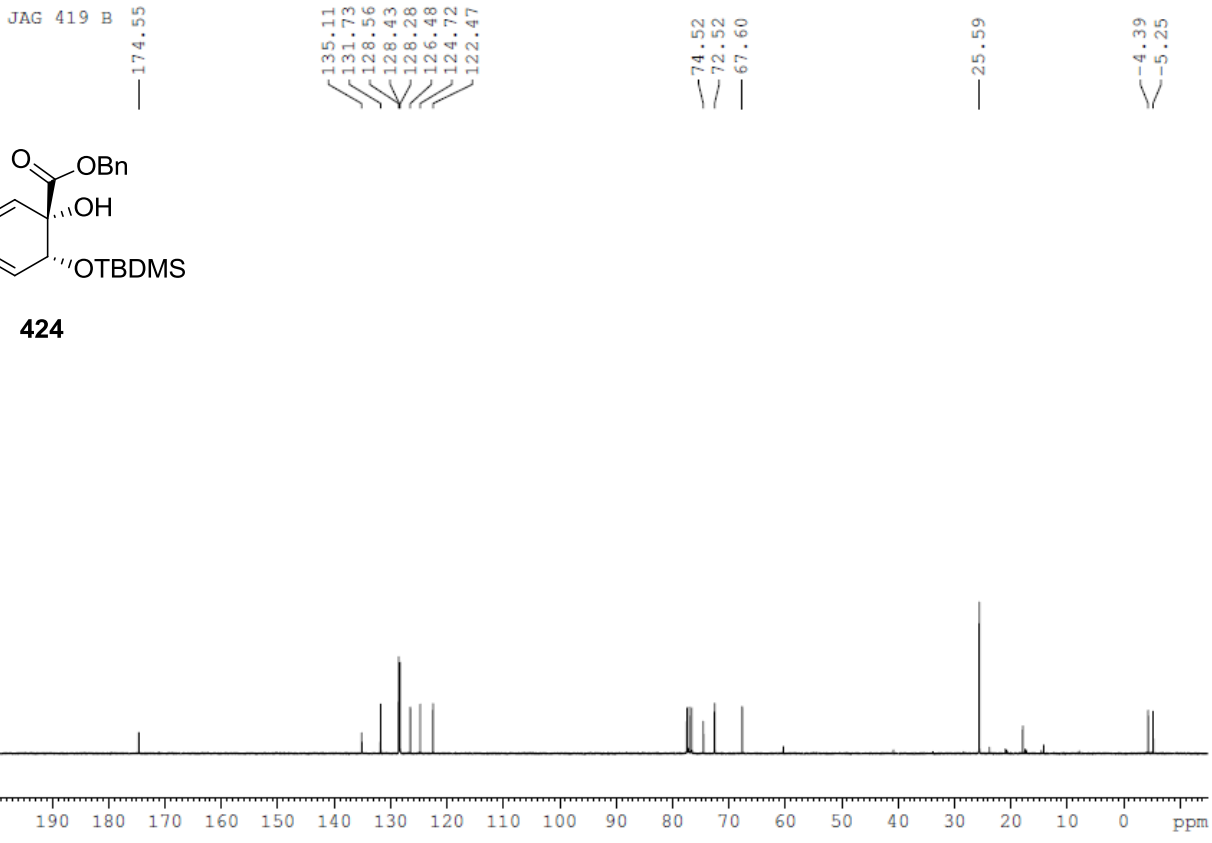

JAG 419 A
174.43
135.50
135.15
128.60
128.47
128.30
127.04
125.86
121.58
77.68
73.80
67.24
25.68
25.68
18.67
17.97
-3.01
-3.14
-4.39
-4.91
O
OBn
OTBDMS
OTBDMS
423
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


JAG 419 A
O
OBn
OTBDMS
OTBDMS
COSY
423
8
7
6
5
4
3
2
1
0

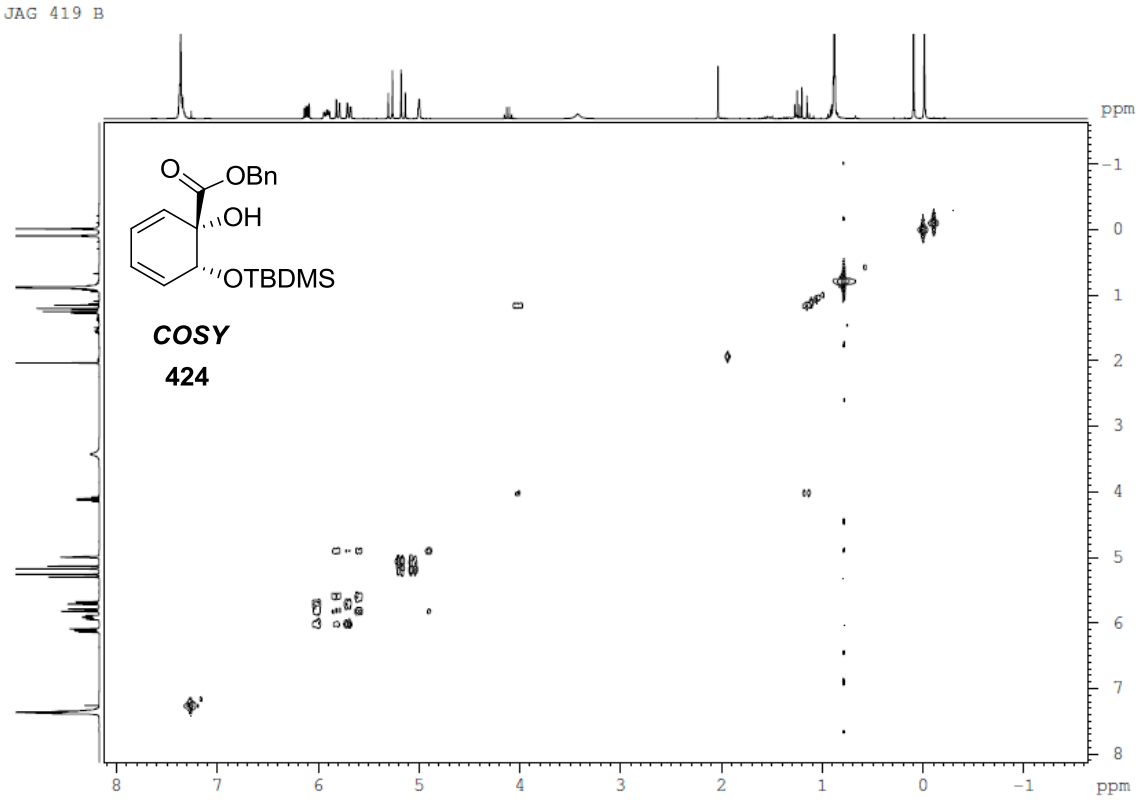

JAG 419 A
O
OBn
OTBDMS
OTBDMS
HSQC
423
ppm
0
20
40
60
80
100
120
140
160
180
8
7
6
5
4
3
2
1
0
ppm

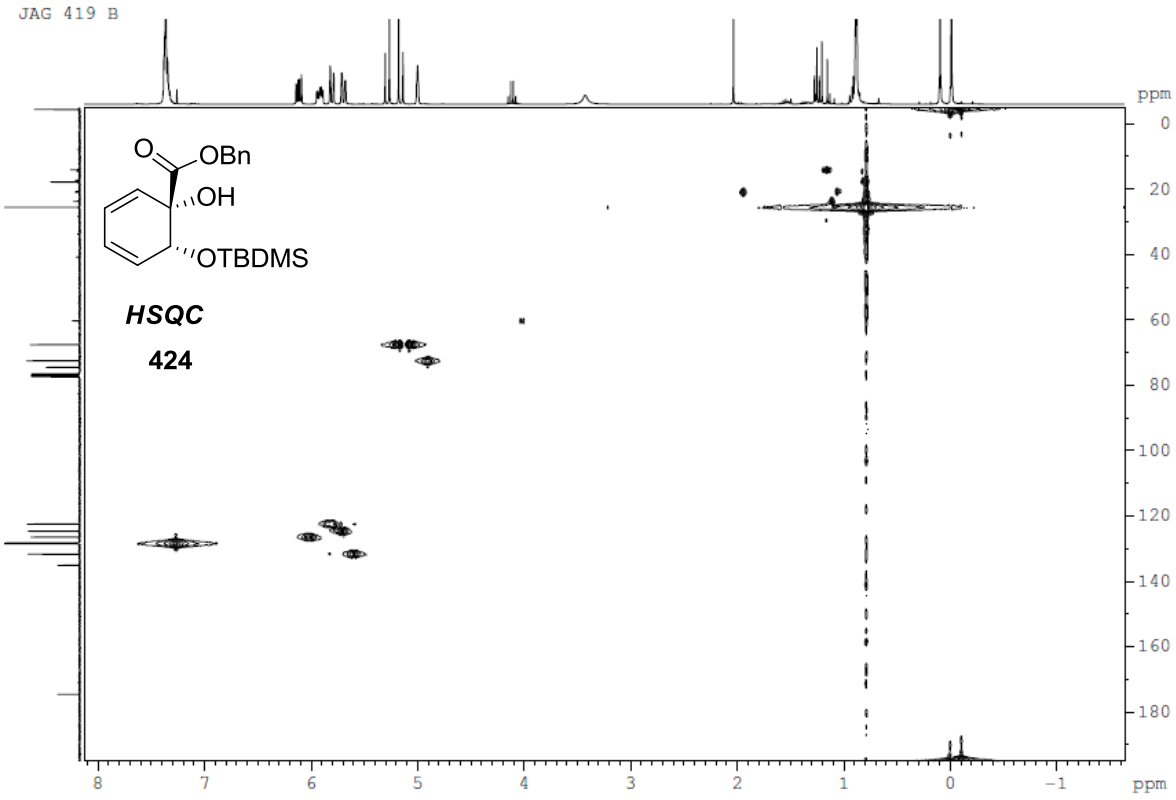

JAG 419 B
6.105
6.088
5.947
5.943
5.938
5.934
5.929
5.926
5.920
5.915
5.911
5.905
5.902
5.897
5.893
5.888
5.884
5.819
5.816
5.787
5.784
5.712
5.708
5.705
5.679
5.676
5.672
5.302
5.261
5.175
5.134
5.006
4.997
4.988
0.883
0.094
-0.012
O
OBn
OH
OTBDMS
6.1
6.0
5.9
5.8
5.7
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
5.02
1.00
1.00
0.99
1.01
2.03
0.98
9.50
3.00
3.02

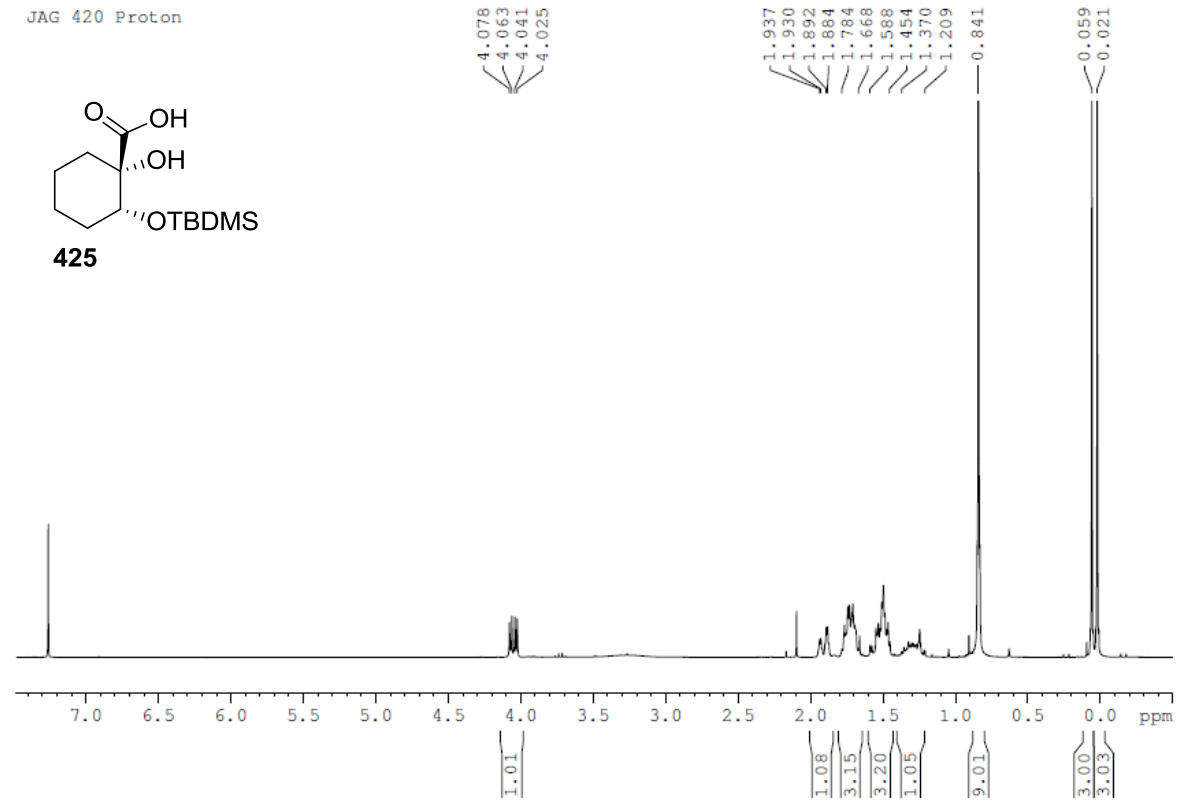
424

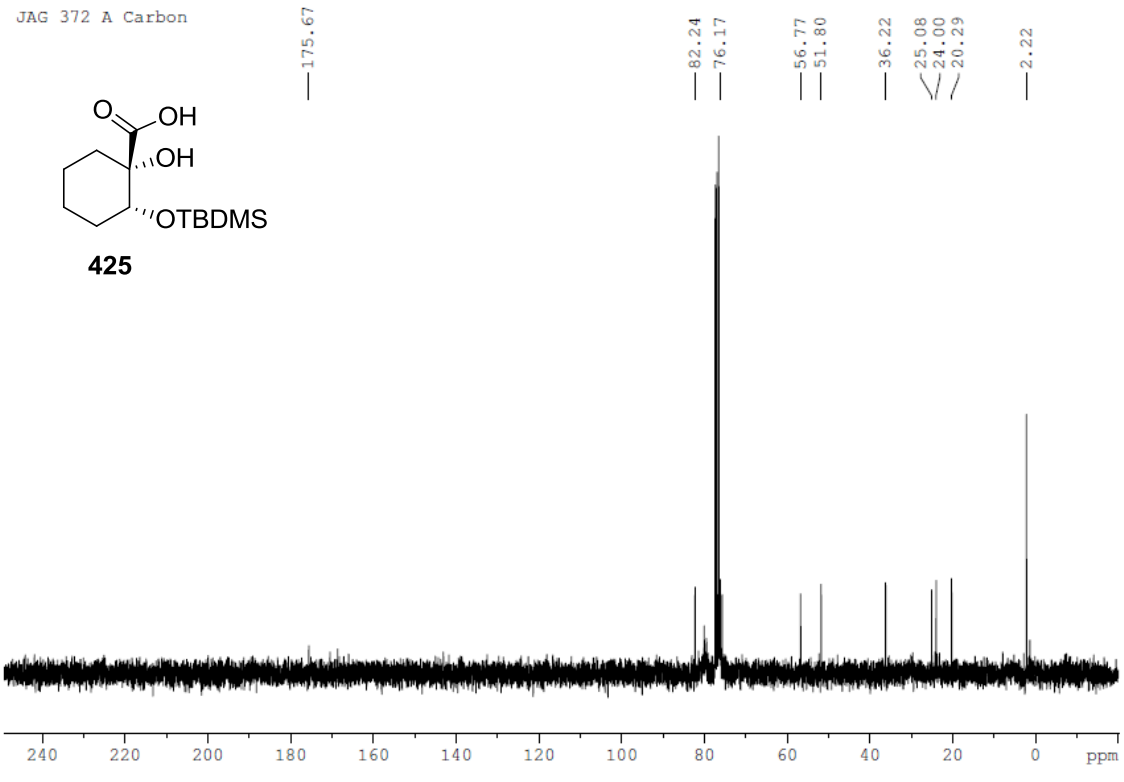

JAG 419 B
174.55
135.11
131.73
128.56
128.43
128.28
126.48
124.72
122.47
74.52
72.52
67.60
25.59
-4.39
-5.25
O
OBn
OH
OTBDMS
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

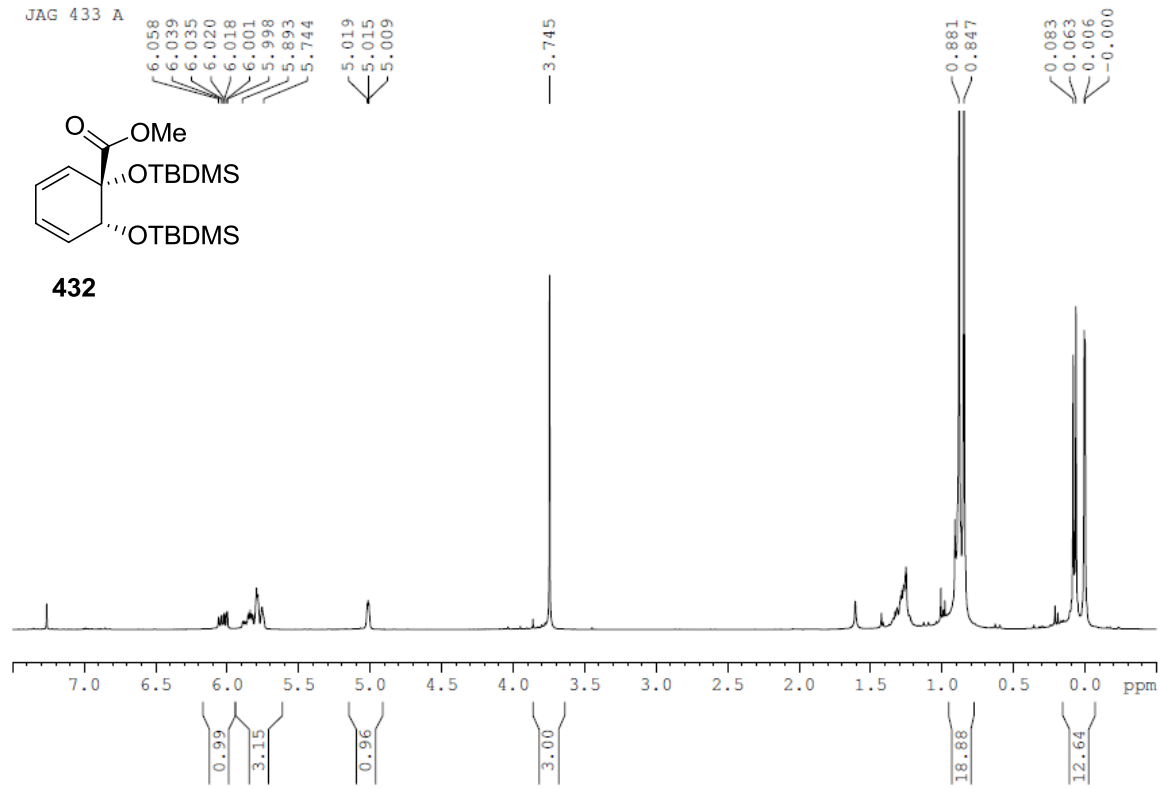
424


JAG 419 B
OBn
OH
OTBDMS
COSY
424
ppm

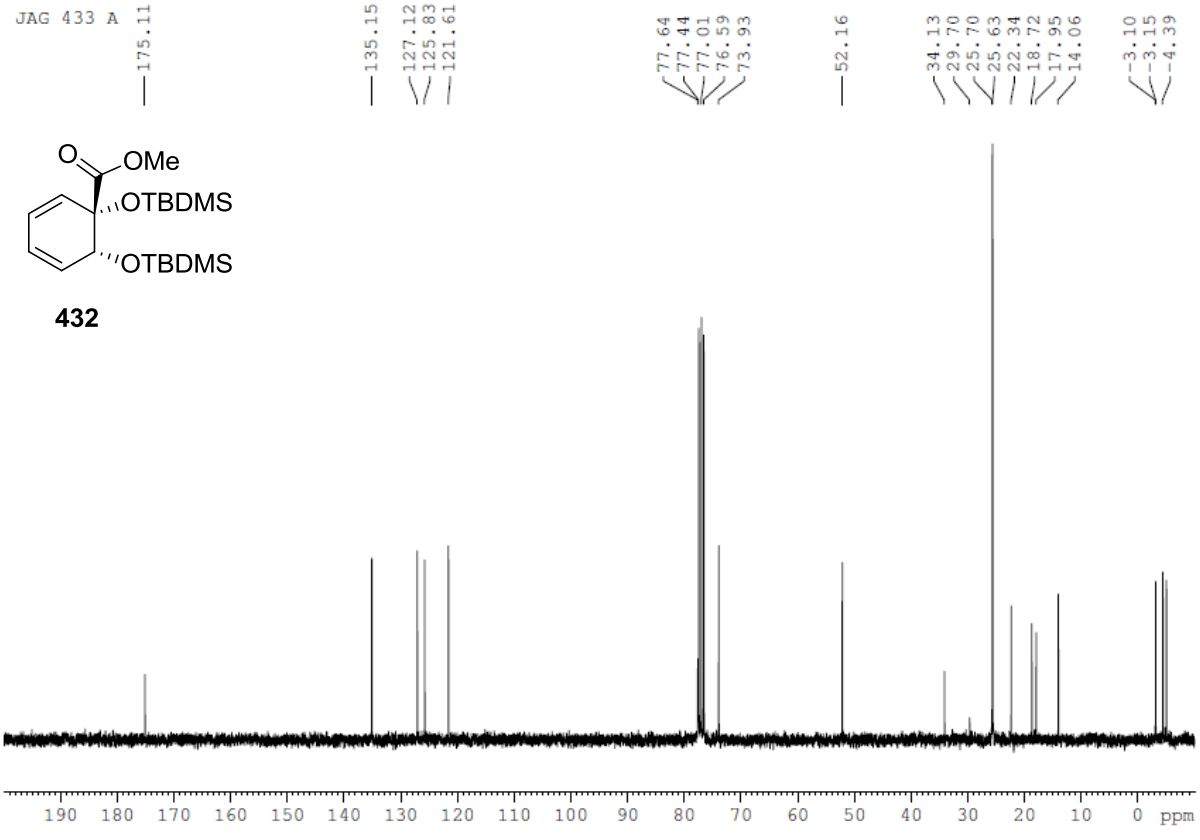

JAG 419 B
OBn
OH
OTBDMS
HSQC
424
ppm


JAG 420 Proton
4.078
4.063
4.041
4.025
1.937
1.930
1.892
1.884
1.784
1.668
1.588
1.454
1.370
1.209
0.841
0.059
0.021
OH
OH
OTBDMS
425
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.01
1.08
3.15
3.20
1.05
9.01
3.00
3.03

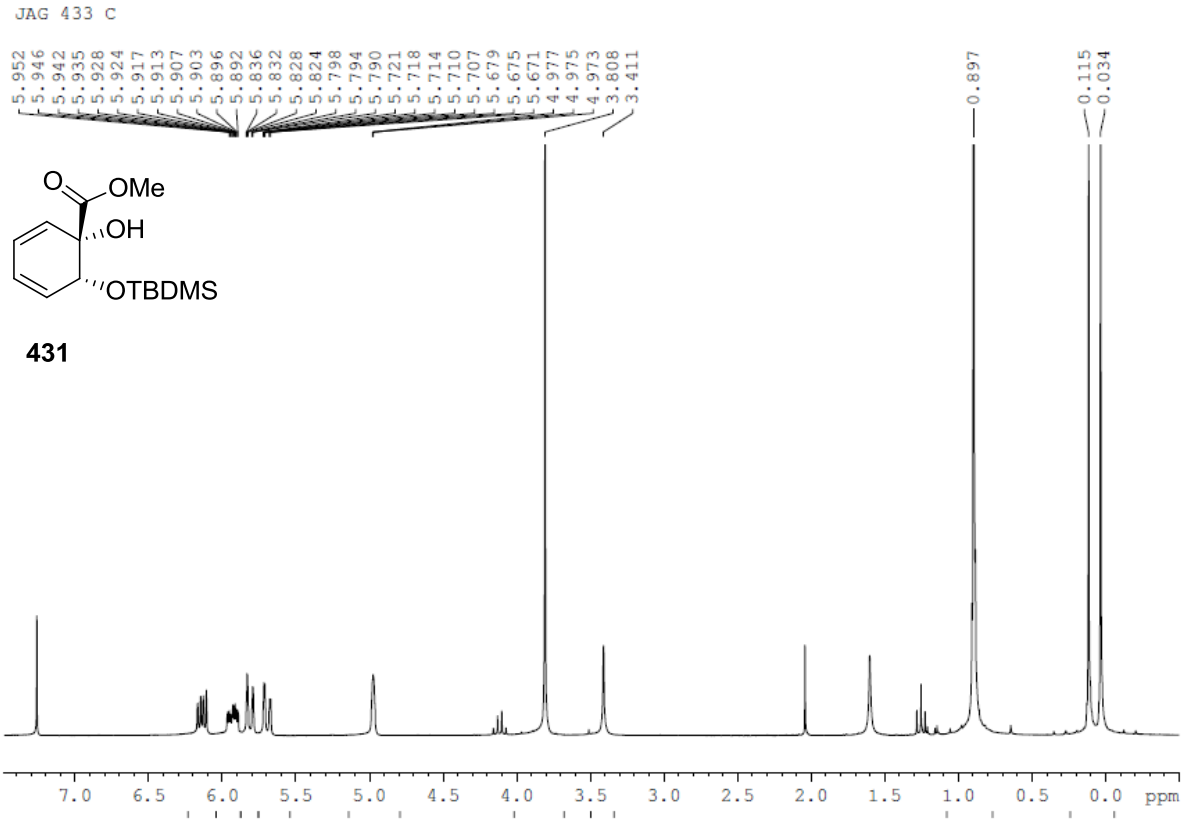

JAG 372 A Carbon
175.67
82.24
76.17
56.77
51.80
36.22
25.08
24.00
20.29
2.22
OH
OH
OTBDMS
425
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


JAG 433 A
6.058
6.039
6.035
6.020
6.018
6.001
5.998
5.893
5.744
5.019
5.015
5.009
3.745
0.881
0.847
0.083
0.063
0.006
-0.000
O
OMe
OTBDMS
OTBDMS
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.99
3.15
0.96
3.00
18.88
12.64

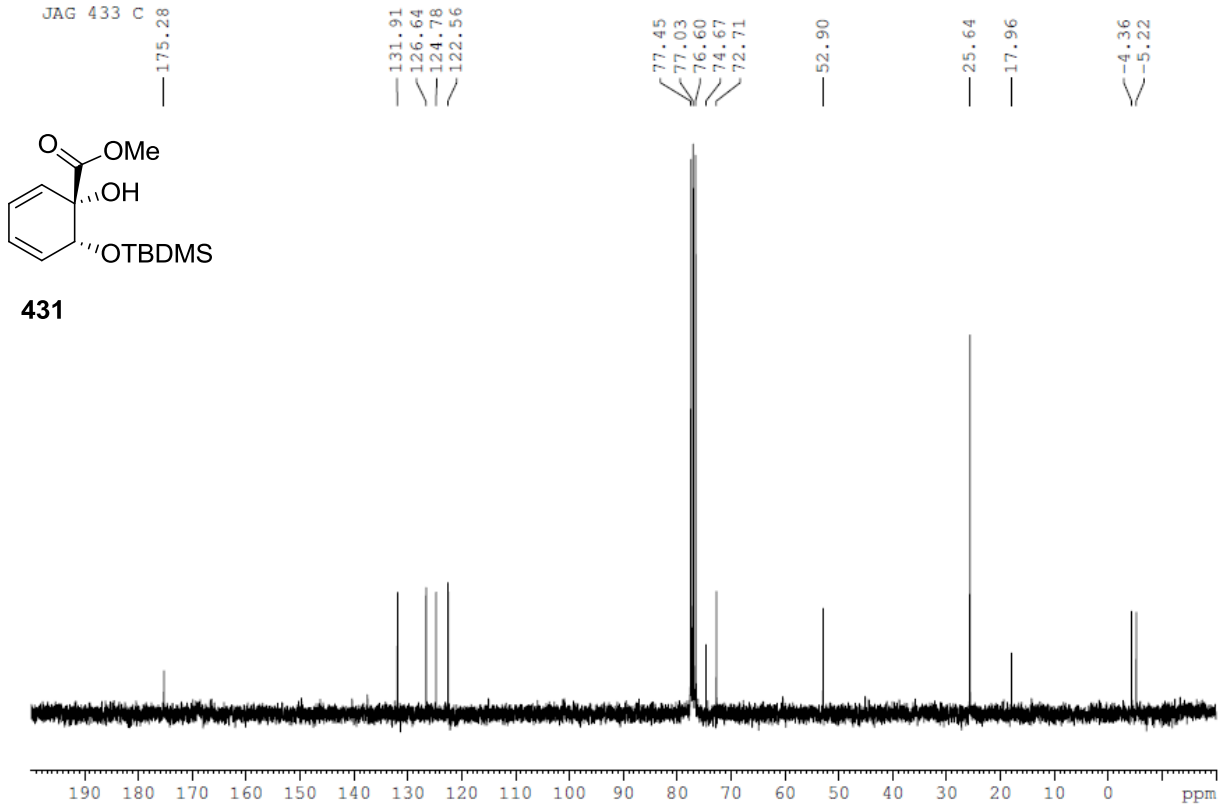
432


JAG 433 A
175.11
135.15
127.12
125.83
121.61
77.64
77.44
77.01
76.59
73.93
52.16
34.13
29.70
25.70
25.63
22.34
18.72
17.95
14.06
-3.10
-3.15
-4.39
O
OMe
OTBDMS
OTBDMS
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

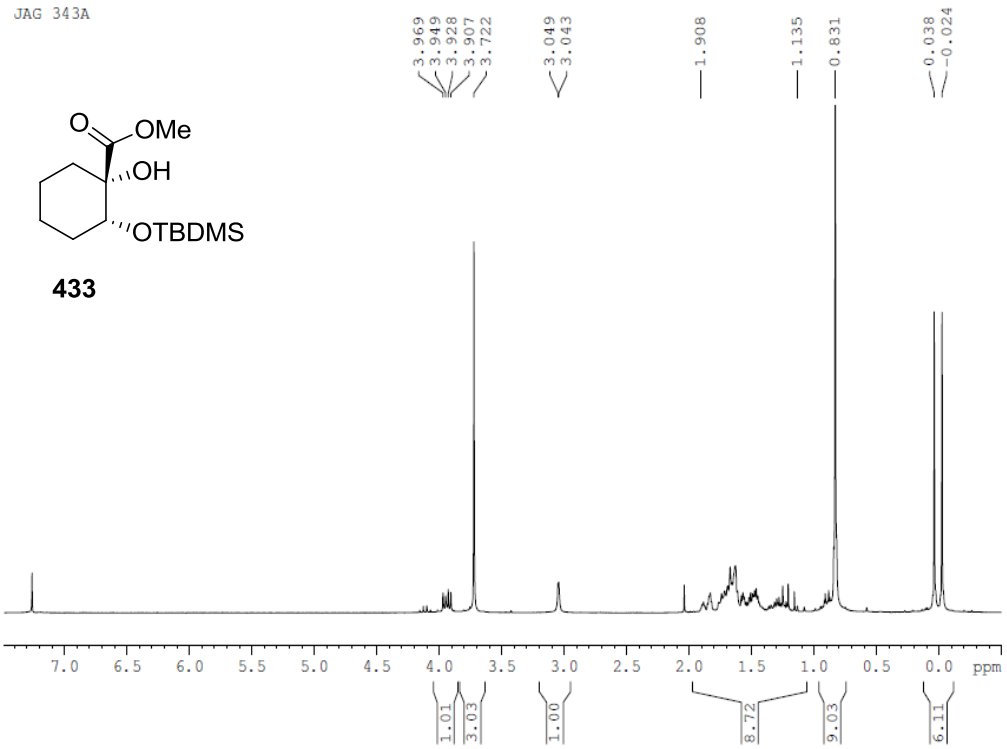
432


JAG 433 C
5.952
5.946
5.942
5.935
5.928
5.924
5.917
5.913
5.907
5.903
5.896
5.892
5.836
5.832
5.828
5.824
5.798
5.794
5.790
5.721
5.718
5.714
5.710
5.707
5.679
5.675
5.671
4.977
4.975
4.973
3.808
3.411
0.897
0.115
0.034
O
OMe
OH
OTBDMS
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

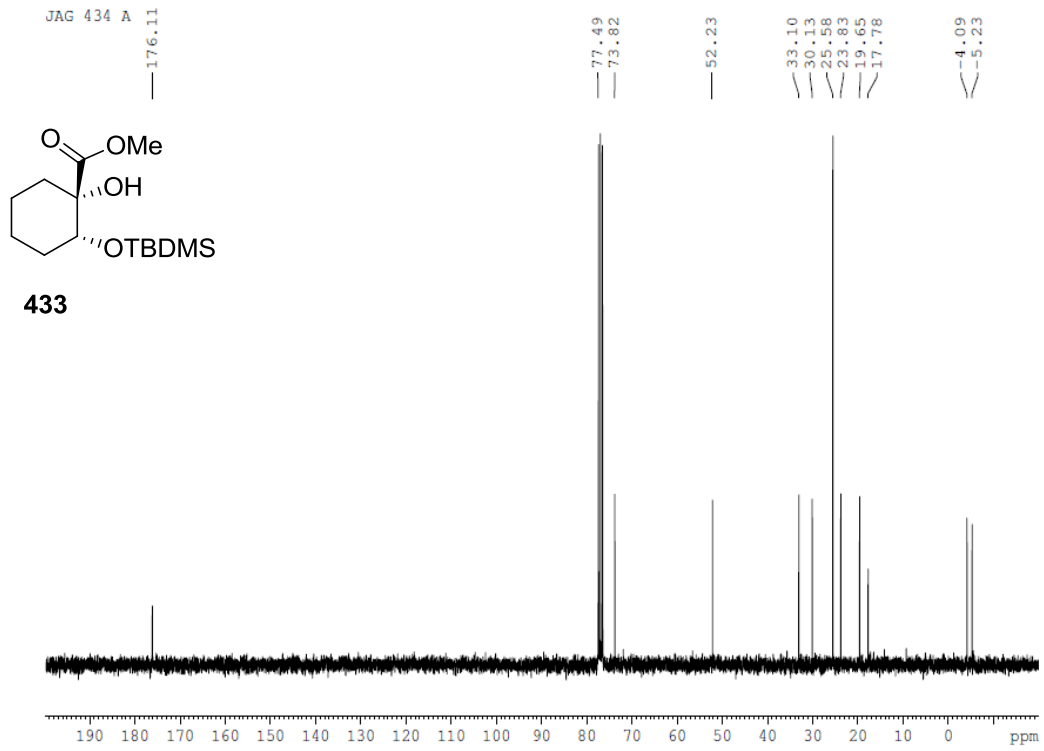
431


JAG 433 C
175.28
131.91
126.64
124.78
122.56
77.45
77.03
76.60
74.67
72.71
52.90
25.64
17.96
-4.36
-5.22
O
OMe
OH
OTBDMS
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

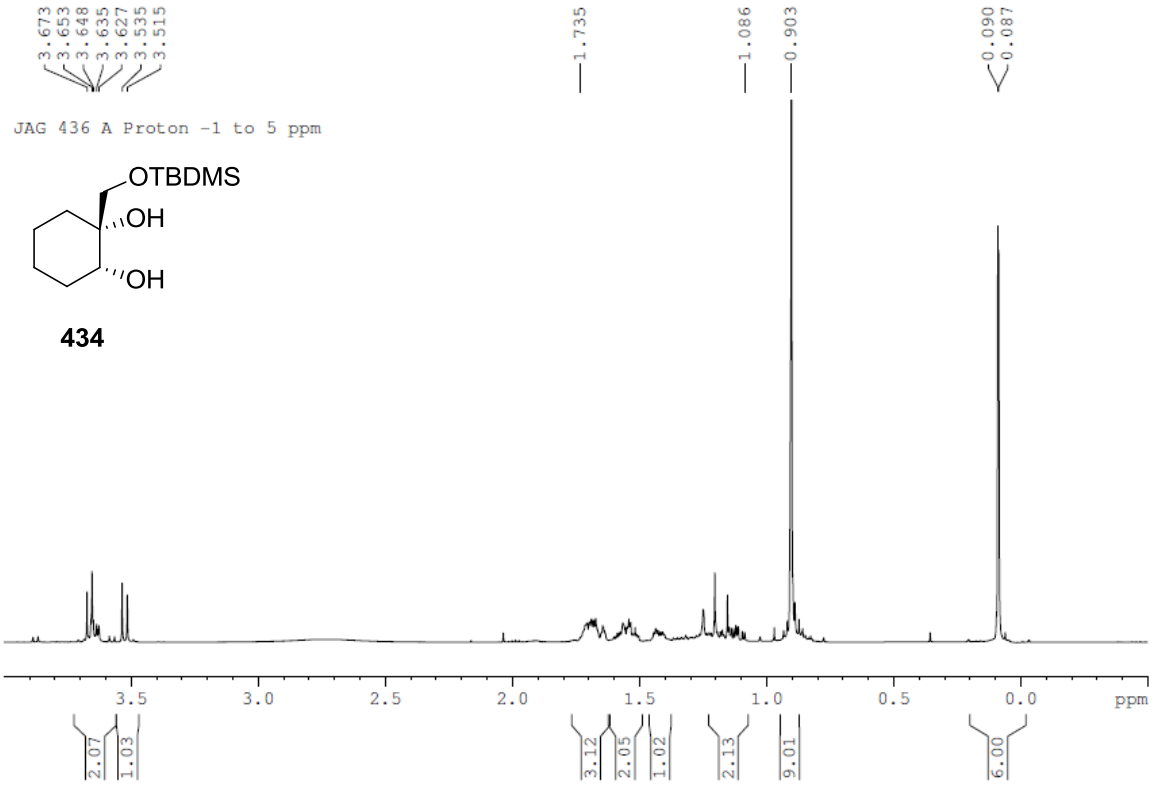
431

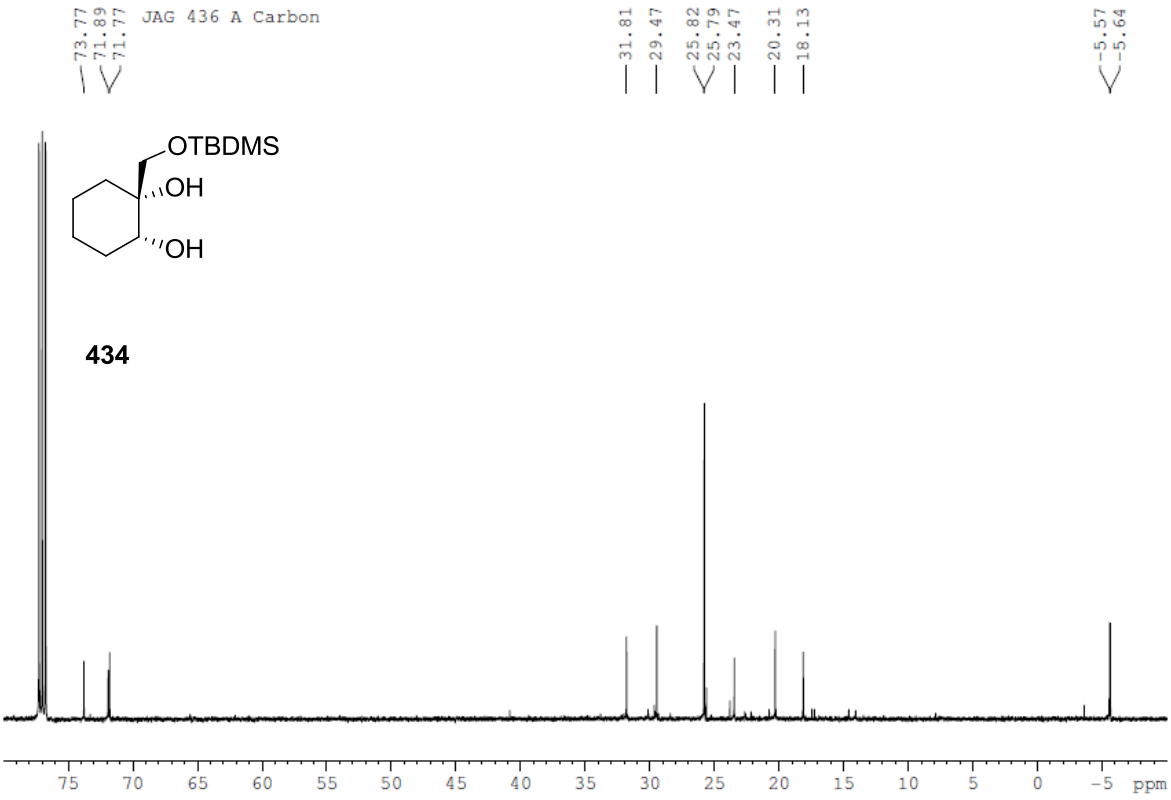

JAG 343A
3.969
3.949
3.928
3.907
3.722
3.049
3.043
1.908
1.135
0.831
0.038
-0.024
OMe
OH
OTBDMS
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.01
3.03
1.00
8.72
9.03
6.11

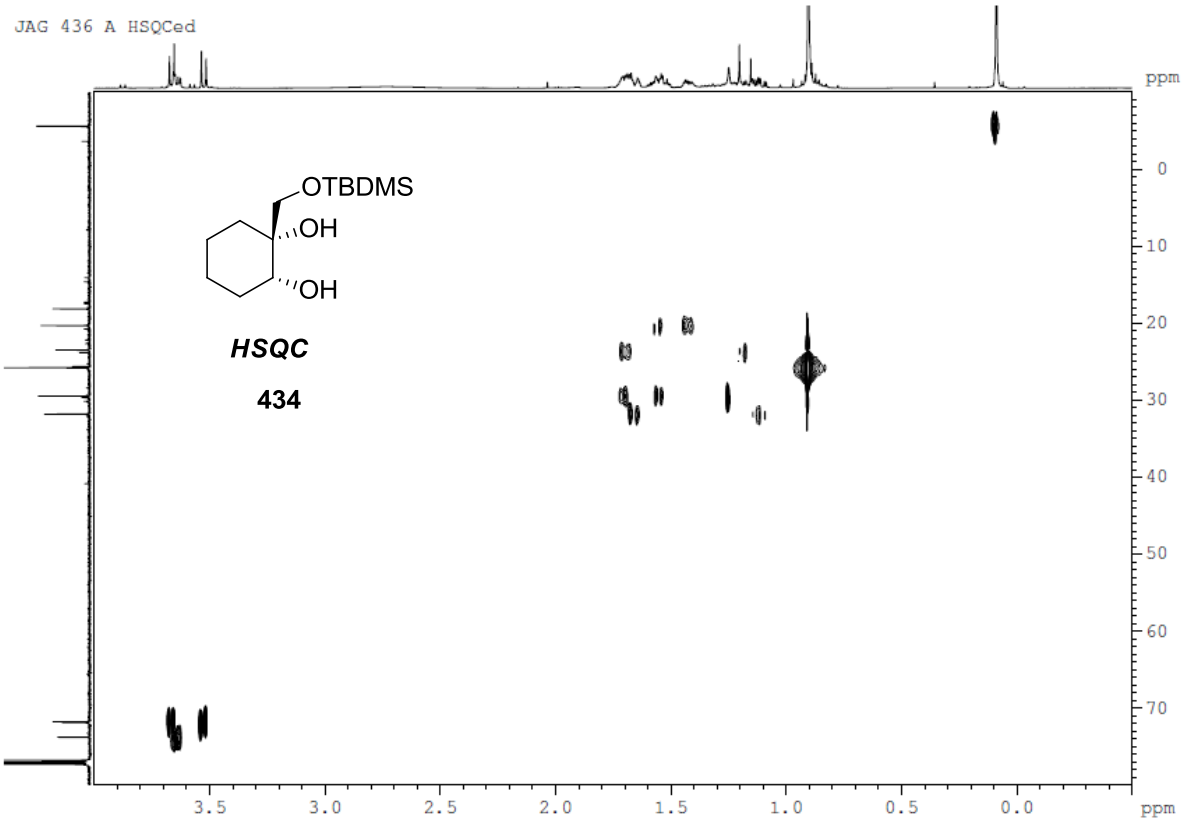
433

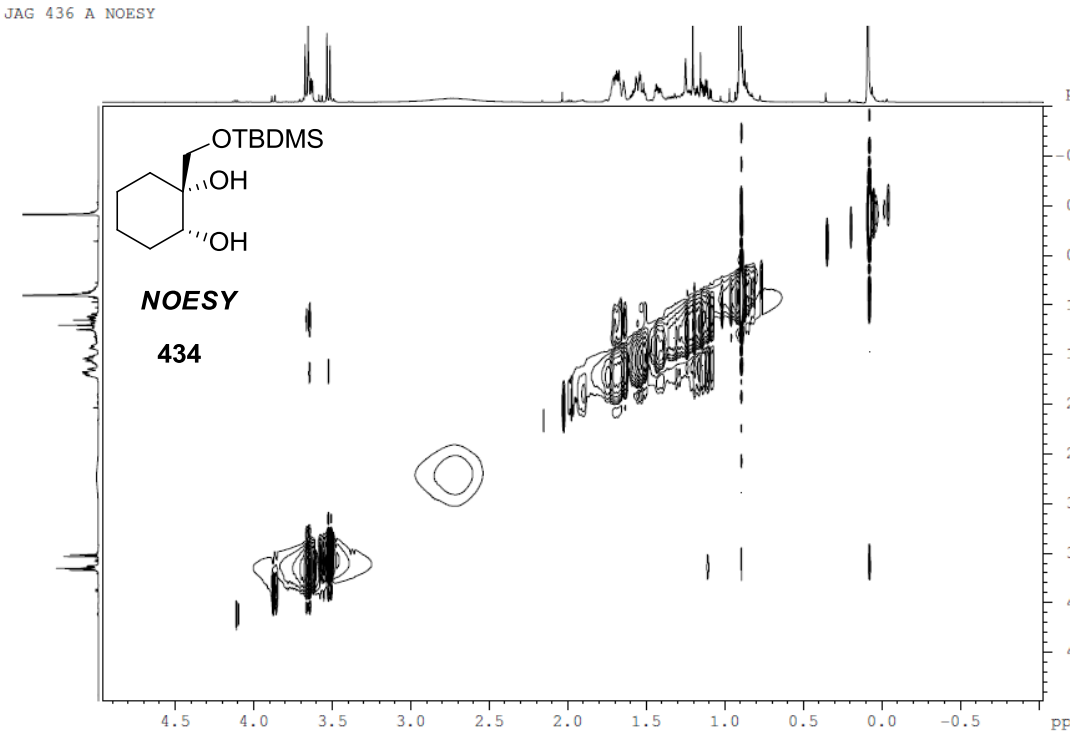

JAG 434 A
176.11
77.49
73.82
52.23
33.10
30.13
25.58
23.83
19.65
17.78
-4.09
-5.23
OMe
OH
OTBDMS
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

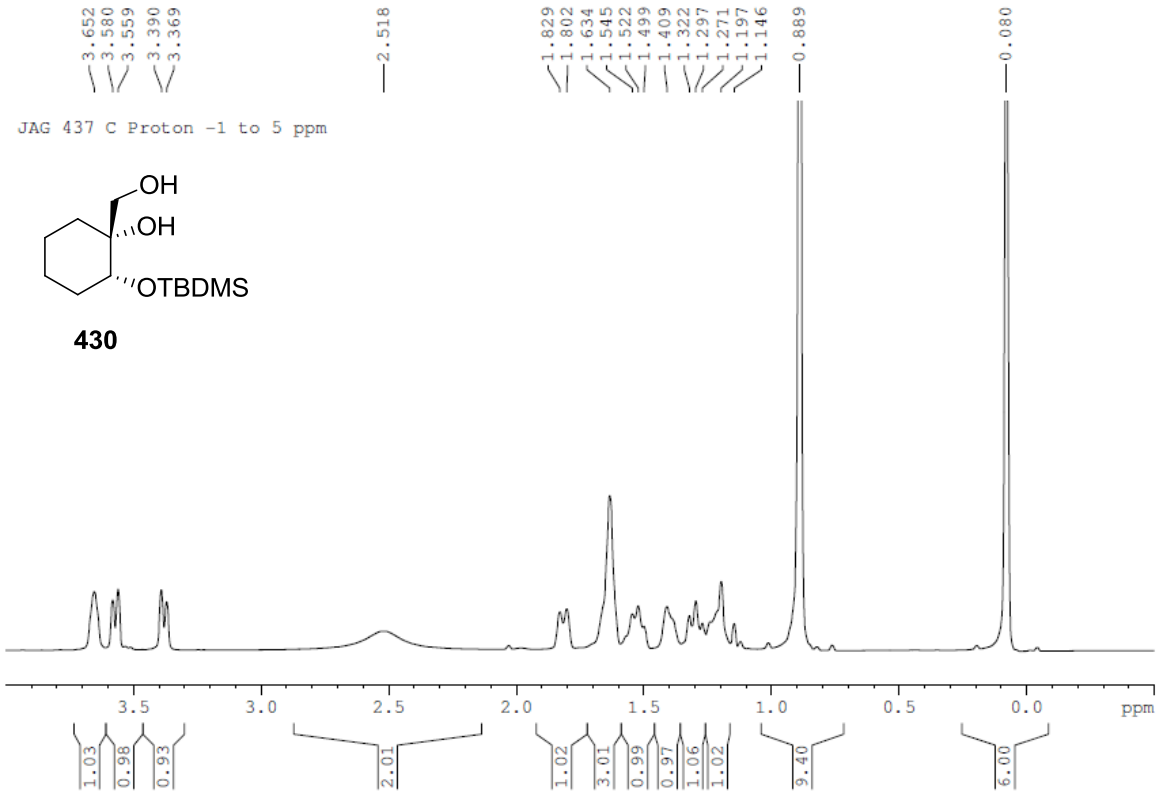
433

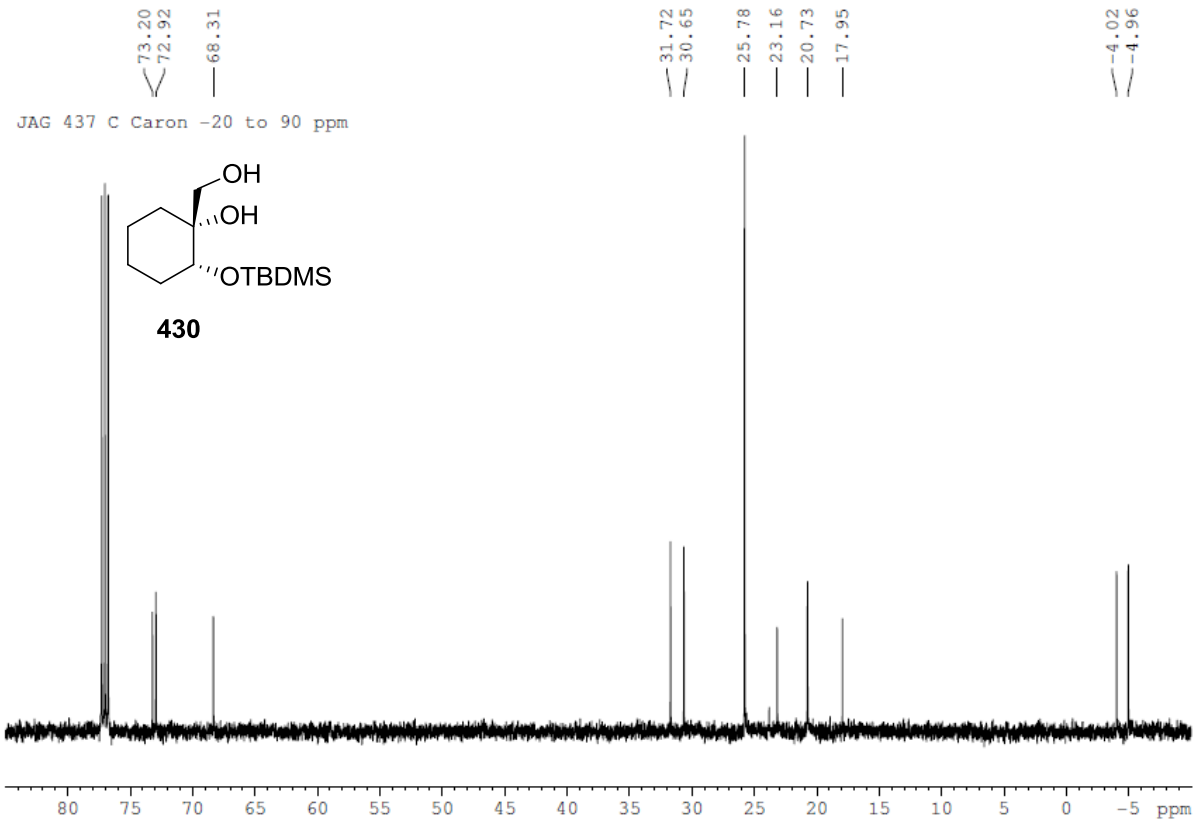

3.673
3.653
3.648
3.635
3.627
3.535
3.515
1.735
1.086
0.903
0.090
0.087
JAG 436 A Proton -1 to 5 ppm
OTBDMS
OH
OH
434
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.07
1.03
3.12
2.05
1.02
2.13
9.01
6.00

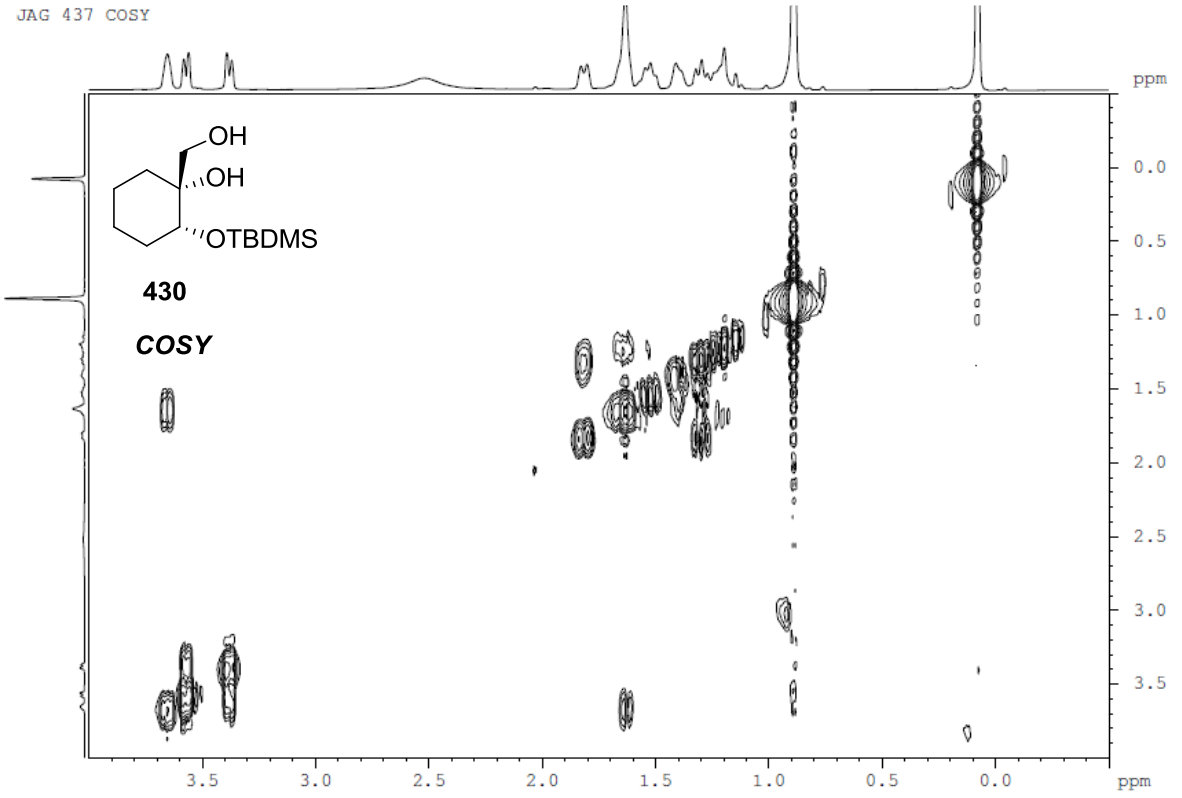

73.77
71.89
71.77
JAG 436 A Carbon
31.81
29.47
25.82
25.79
23.47
20.31
18.13
-5.57
-5.64
OTBDMS
OH
OH
434
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
ppm

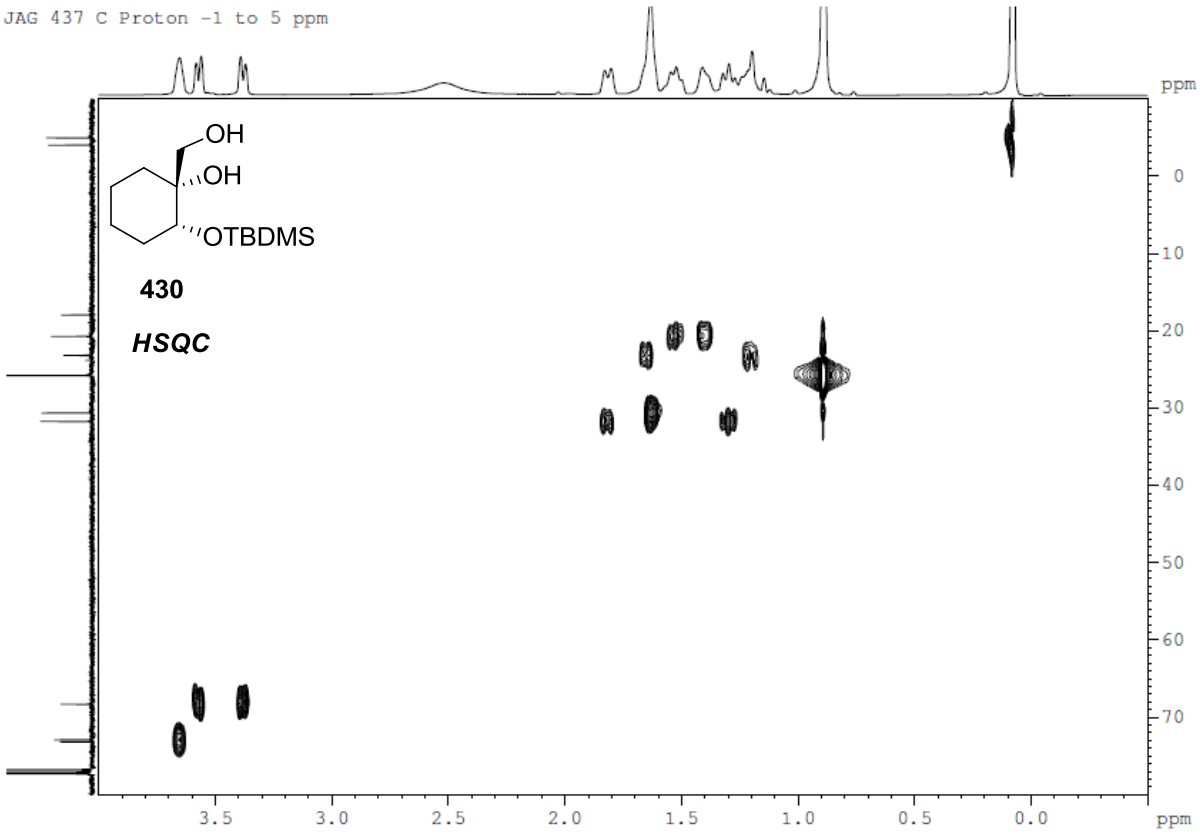

JAG 436 A HSQCed
OTBDMS
OH
OH
HSQC
434
ppm
0
10
20
30
40
50
60
70
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

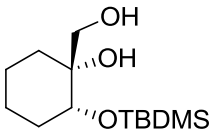

JAG 436 A NOESY
OTBDMS
OH
OH
NOESY
434
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


3.652
3.580
3.559
3.390
3.369
2.518
1.829
1.802
1.634
1.545
1.522
1.499
1.409
1.322
1.297
1.271
1.197
1.146
0.889
0.080
JAG 437 C Proton -1 to 5 ppm
OH
OH
OTBDMS
430
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.03
0.98
0.93
2.01
1.02
3.01
0.99
0.97
1.06
1.02
9.40
6.00


73.20
72.92
68.31
31.72
30.65
25.78
23.16
20.73
17.95
-4.02
-4.96
JAG 437 C Caron -20 to 90 ppm
OH
OH
OTBDMS
430
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
ppm

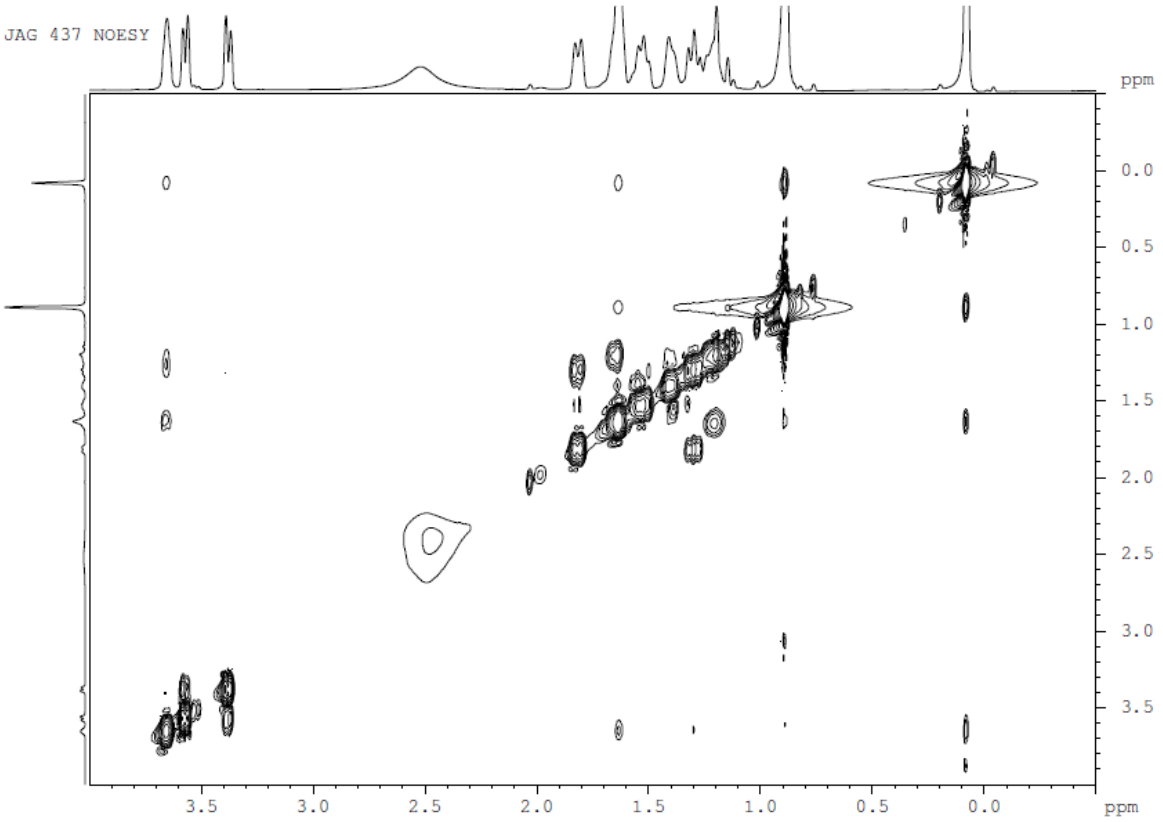

JAG 437 COSY
OH
OH
OTBDMS
430
COSY
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

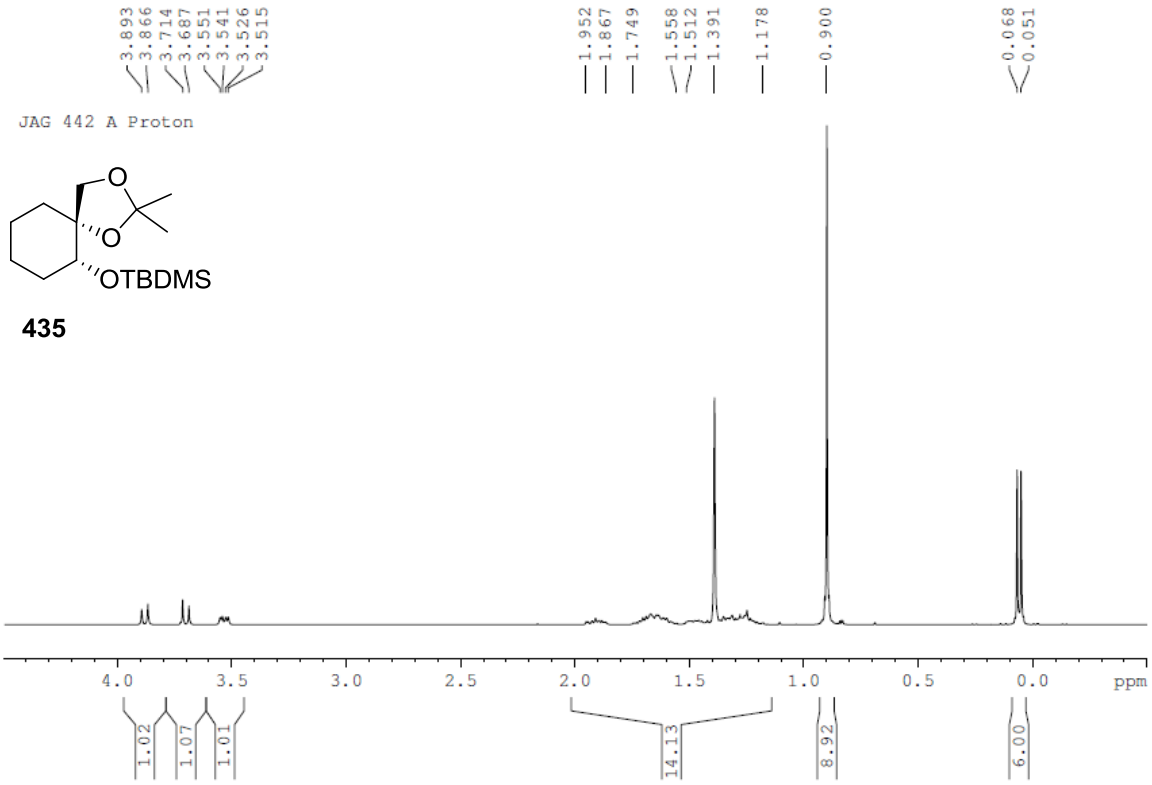

JAG 437 C Proton -1 to 5 ppm
OH
OH
OTBDMS
430
HSQC
ppm
0
10
20
30
40
50
60
70
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

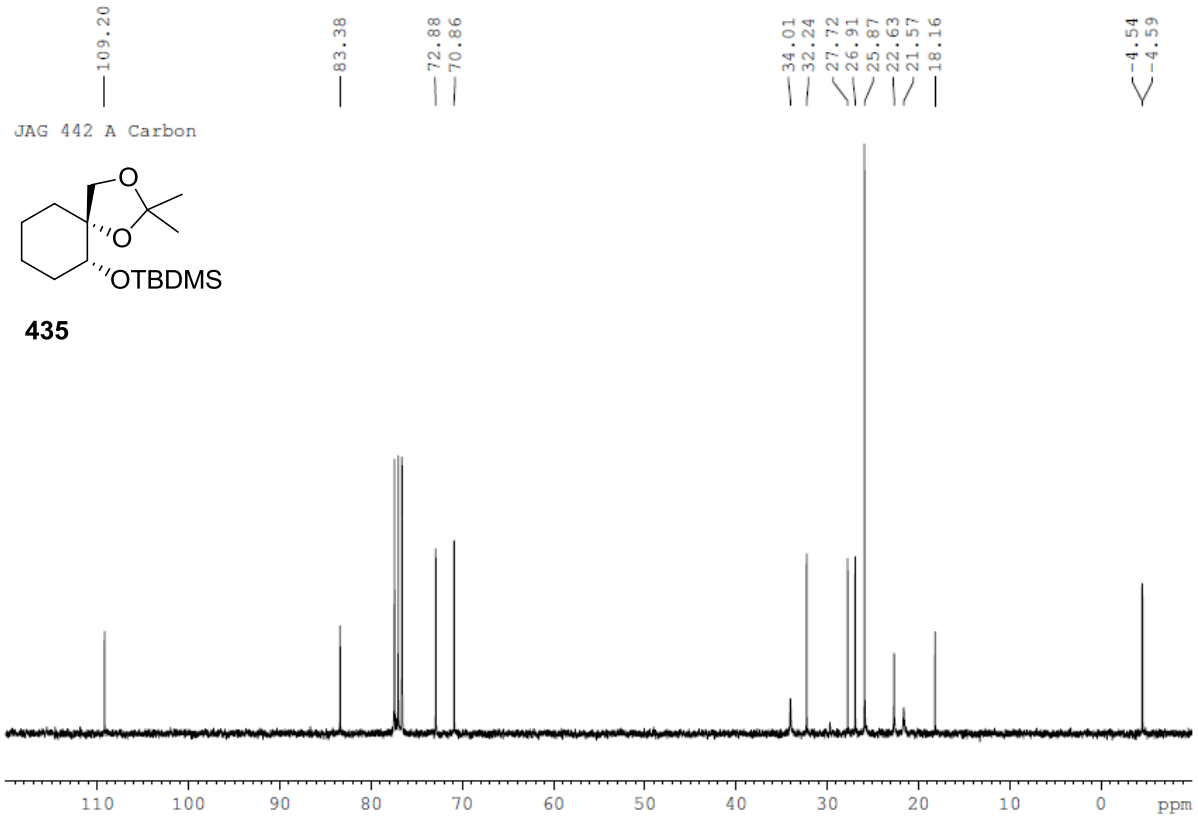

OH
OH
OTBDMS

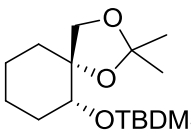
430

NOESY


JAG 437 NOESY
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

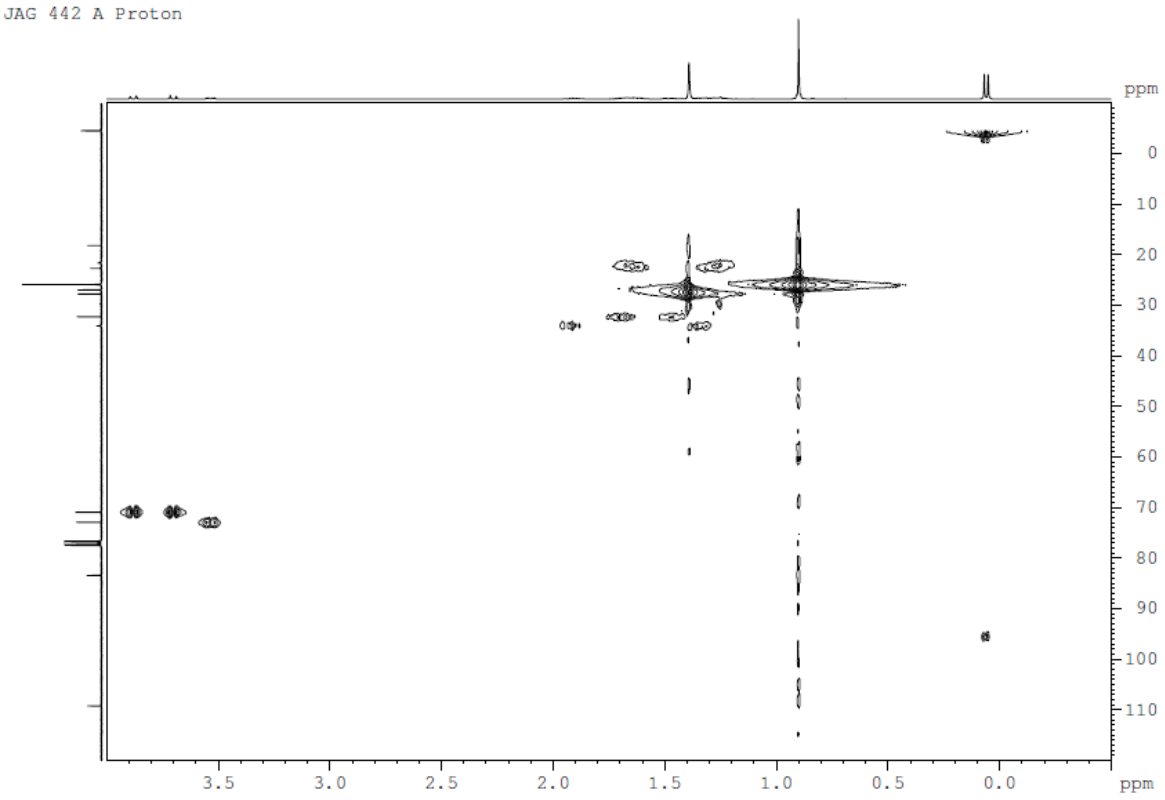

3.893
3.866
3.714
3.687
3.551
3.541
3.526
3.515
1.952
1.867
1.749
1.558
1.512
1.391
1.178
0.900
0.068
0.051
JAG 442 A Proton
O
O
OTBDMS
435
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.02
1.07
1.01
14.13
8.92
6.00

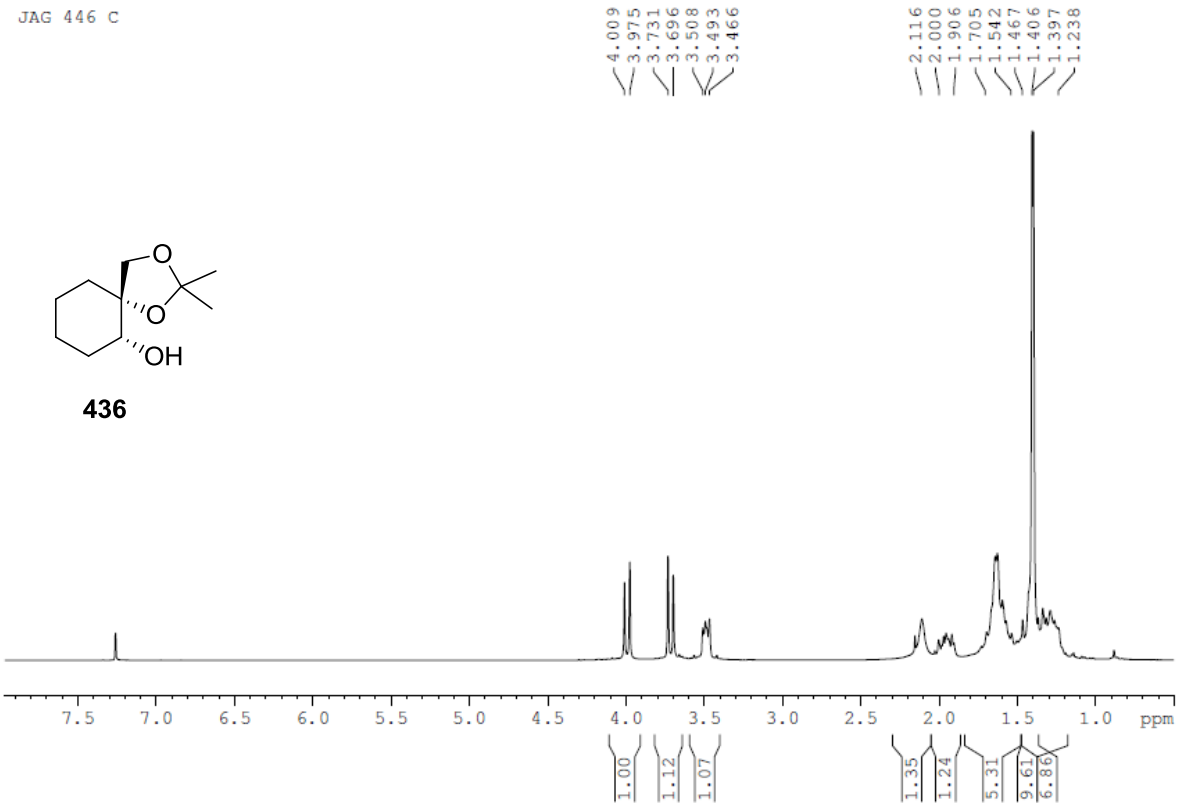

109.20
83.38
72.88
70.86
34.01
32.24
27.72
26.91
25.87
22.63
21.57
18.16
-4.54
-4.59
JAG 442 A Carbon
O
O
OTBDMS
435
110
100
90
80
70
60
50
40
30
20
10
0
ppm


O
O
OTBDMS

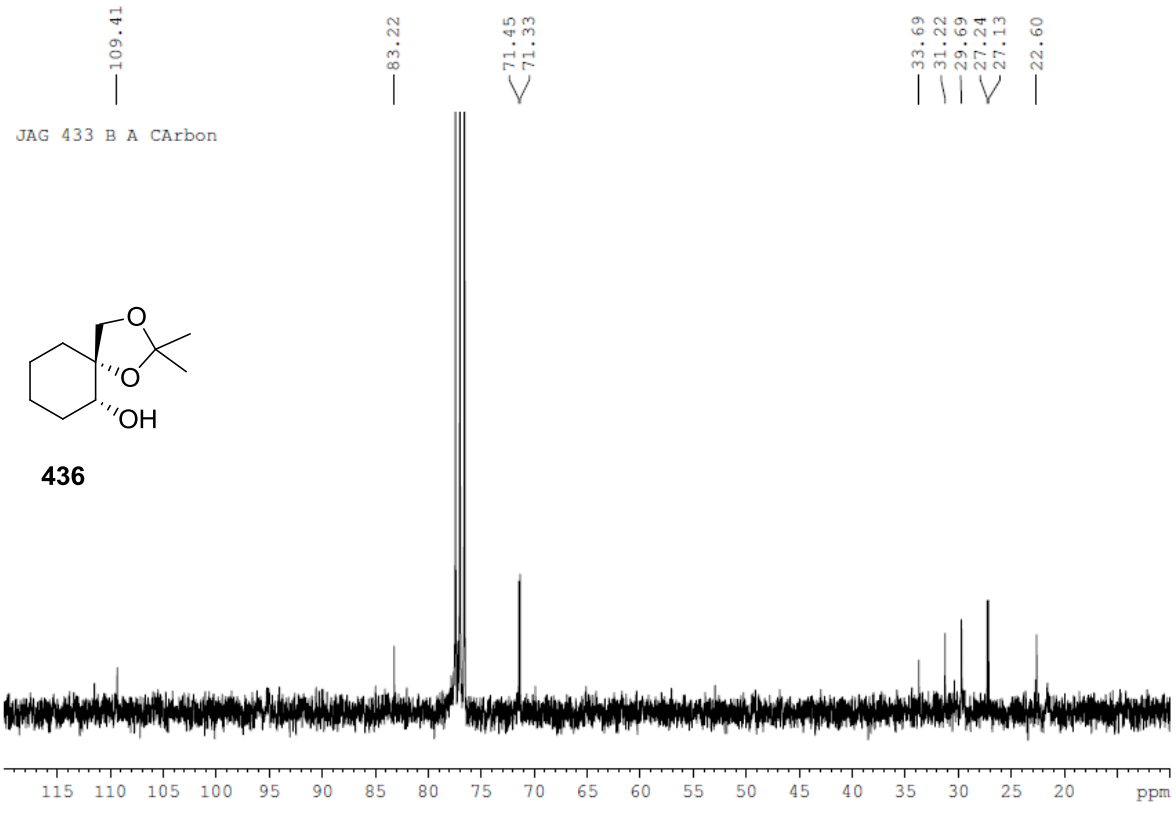
435

HSQC

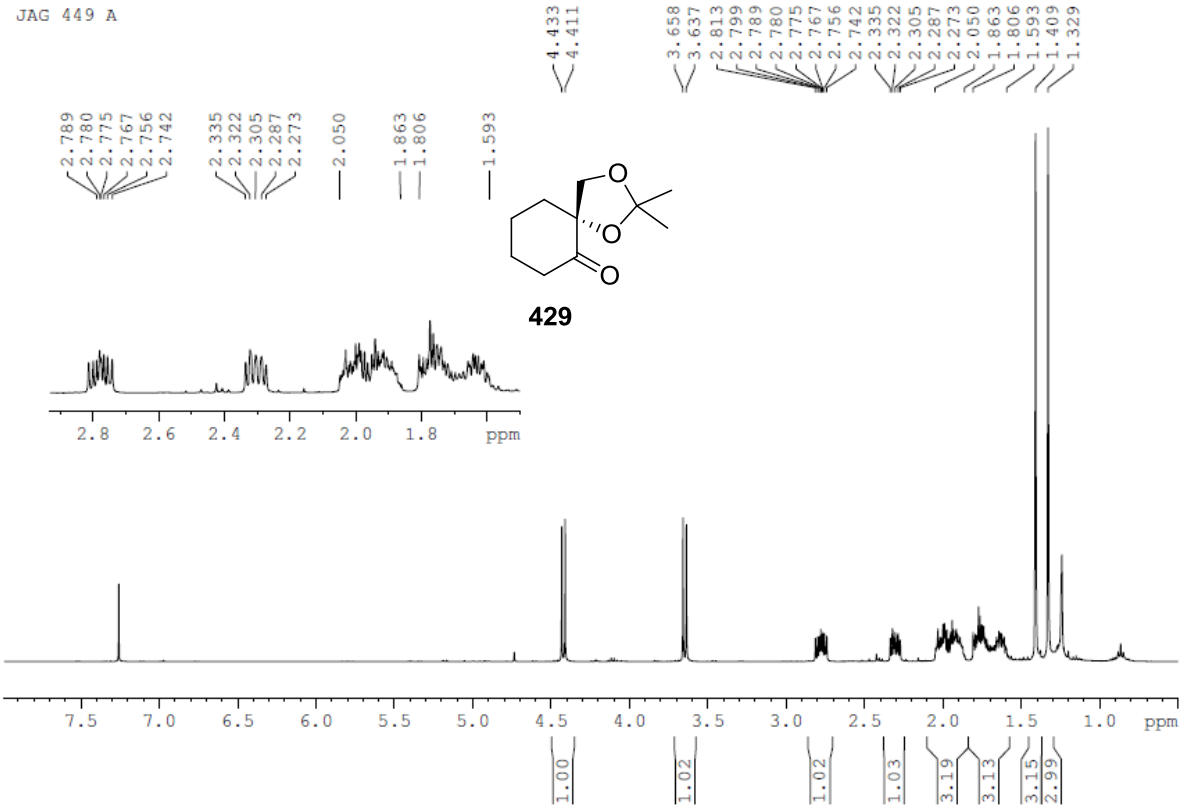

JAG 442 A Proton
ppm
0
10
20
30
40
50
60
70
80
90
100
110
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

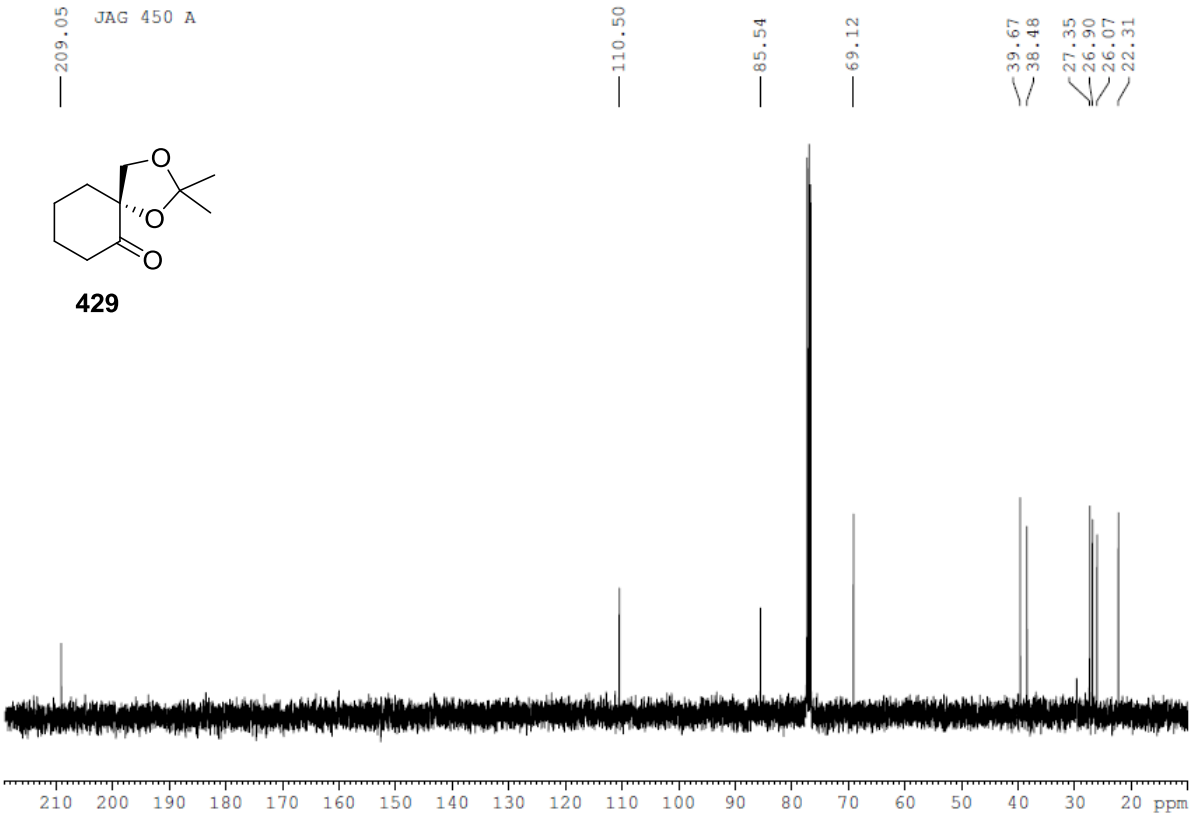

JAG 446 C
4.009
3.975
3.731
3.696
3.508
3.493
3.466
2.116
2.000
1.906
1.705
1.542
1.467
1.406
1.397
1.238
O
O
OH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.12
1.07
1.35
1.24
5.31
9.61
6.86

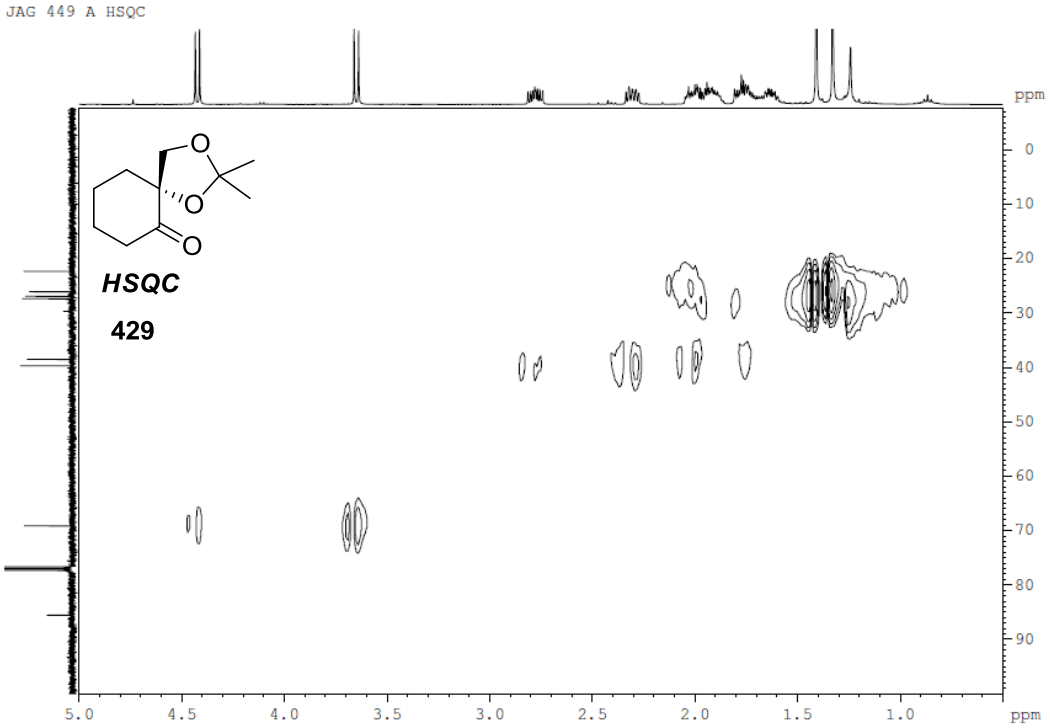
436


109.41
83.22
71.45
71.33
33.69
31.22
29.69
27.24
27.13
22.60
JAG 433 B A CArbon
O
O
OH
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
ppm

436


JAG 449 A
4.433
4.411
3.658
3.637
2.813
2.799
2.789
2.780
2.775
2.767
2.756
2.742
2.335
2.322
2.305
2.287
2.273
2.050
1.863
1.806
1.593
1.409
1.329
429
ppm
1.00
1.02
1.02
1.03
3.19
3.13
3.15
2.99


JAG 450 A
209.05
110.50
85.54
69.12
39.67
38.48
27.35
26.90
26.07
22.31
429
ppm


JAG 449 A HSQC
HSQC
429
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

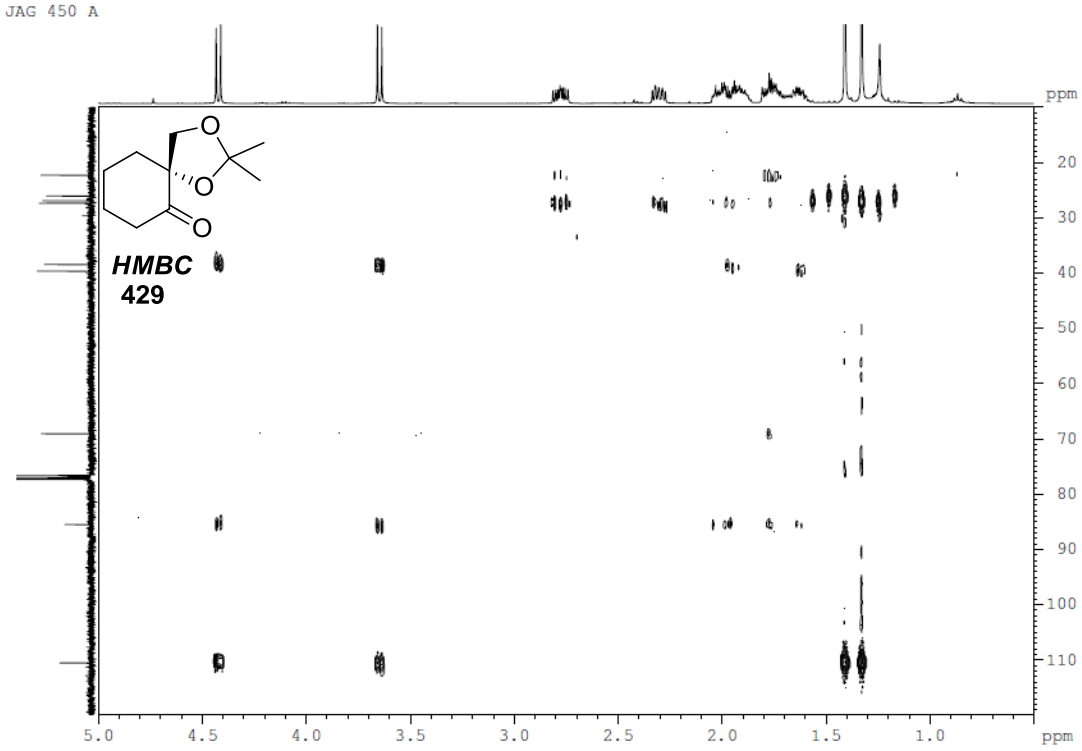

JAG 450 A
HMBC
429
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

Table s1. Crystal data and structure refinement for **55**.

Identification code	h11sel3
Empirical formula	C_{11} H_{15} N O_7
Formula weight	273.24
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_1$ 2_1 2_1
Unit cell dimensions	a = 5.88820(10) A alpha = 90 deg. b = 14.2027(3) A beta = 90 deg. c = 14.2431(2) A gamma = 90 deg.
Volume	1191.13(4) A^3
Z, Calculated density	4, 1.524 Mg/m^3
Absorption coefficient	0.129 mm^-1
F(000)	576
Crystal size	0.60 x 0.50 x 0.50 mm
Theta range for data collection	3.75 to 30.07 deg.
Limiting indices	-8<=h<=8, -20<=k<=20, -20<=l<=20
Reflections collected / unique	25859 / 3476 [R(int) = 0.0511]
Completeness to theta = 30.07	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9385 and 0.9268
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3476 / 0 / 182
Goodness-of-fit on F^2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0801
R indices (all data)	R1 = 0.0454, wR2 = 0.0857
Absolute structure parameter	-0.1(7)
Largest diff. peak and hole	0.219 and -0.213 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for h11sel3. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	1931(2)	5240(1)	3519(1)	34(1)
O(1)	4539(2)	6665(1)	1634(1)	33(1)
O(2)	7757(1)	5897(1)	2052(1)	23(1)
O(3)	8245(2)	3890(1)	2293(1)	42(1)
O(4)	4072(2)	4759(1)	3783(1)	30(1)
O(5)	5879(2)	6169(1)	4883(1)	28(1)
O(6)	2764(2)	6936(1)	4464(1)	37(1)
O(7)	3396(2)	6626(1)	5977(1)	39(1)
C(1)	6861(2)	6548(1)	1373(1)	27(1)
C(2)	8082(3)	7479(1)	1495(1)	38(1)
C(3)	7059(3)	6160(1)	384(1)	39(1)
C(4)	5970(2)	5301(1)	2376(1)	22(1)
C(5)	6188(2)	4312(1)	1972(1)	32(1)
C(6)	6036(2)	5248(1)	3453(1)	22(1)
C(7)	6067(2)	6229(1)	3872(1)	23(1)
C(8)	3963(2)	6576(1)	5169(1)	29(1)
C(9)	3884(2)	6739(1)	3580(1)	27(1)
C(10)	2451(2)	6087(1)	2978(1)	29(1)
C(11)	3784(2)	5831(1)	2090(1)	27(1)

Table 3. Bond lengths [A] for h11sel3.

N(1)-C(10)	1.4614(18)
N(1)-O(4)	1.4820(16)
N(1)-H(1)	0.93(2)
O(1)-C(11)	1.4217(16)
O(1)-C(1)	1.4264(16)
O(2)-C(4)	1.4277(14)
O(2)-C(1)	1.4373(15)
O(3)-C(5)	1.4268(18)
O(3)-H(3)	0.88(3)
O(4)-C(6)	1.4284(15)
O(5)-C(8)	1.3310(16)
O(5)-C(7)	1.4478(14)
O(6)-C(8)	1.3304(17)
O(6)-C(9)	1.4482(15)
O(7)-C(8)	1.2000(17)
C(1)-C(2)	1.5147(19)
C(1)-C(3)	1.5174(18)
C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800
C(2)-H(2C)	0.9800
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-C(5)	1.5241(16)
C(4)-C(6)	1.5353(16)
C(4)-C(11)	1.5461(17)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.5161(16)
C(6)-H(6)	1.0000
C(7)-C(9)	1.5329(17)
C(7)-H(7)	1.0000
C(9)-C(10)	1.5178(18)
C(9)-H(9)	1.0000
C(10)-C(11)	1.5328(18)
C(10)-H(10)	1.0000
C(11)-H(11)	1.0000

Table 4. Bond angles [deg] for h11sel3.

C(10)-N(1)-O(4)	109.56(9)
C(10)-N(1)-H(1)	107.7(12)
O(4)-N(1)-H(1)	101.4(13)
C(11)-O(1)-C(1)	108.79(10)
C(4)-O(2)-C(1)	109.18(9)
C(5)-O(3)-H(3)	111.7(15)
C(6)-O(4)-N(1)	112.42(8)
C(8)-O(5)-C(7)	110.10(10)
C(8)-O(6)-C(9)	109.93(10)
O(1)-C(1)-O(2)	104.56(10)
O(1)-C(1)-C(2)	108.88(11)
O(2)-C(1)-C(2)	108.06(11)
O(1)-C(1)-C(3)	110.97(11)

O(2)-C(1)-C(3)	111.23(11)
C(2)-C(1)-C(3)	112.77(12)
C(1)-C(2)-H(2A)	109.5
C(1)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
C(1)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
C(1)-C(3)-H(3A)	109.5
C(1)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(1)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
O(2)-C(4)-C(5)	111.23(10)
O(2)-C(4)-C(6)	109.52(9)
C(5)-C(4)-C(6)	109.27(9)
O(2)-C(4)-C(11)	103.86(9)
C(5)-C(4)-C(11)	114.76(10)
C(6)-C(4)-C(11)	107.99(10)
O(3)-C(5)-C(4)	109.75(10)
O(3)-C(5)-H(5A)	109.7
C(4)-C(5)-H(5A)	109.7
O(3)-C(5)-H(5B)	109.7
C(4)-C(5)-H(5B)	109.7
H(5A)-C(5)-H(5B)	108.2
O(4)-C(6)-C(7)	109.06(9)
O(4)-C(6)-C(4)	109.40(10)
C(7)-C(6)-C(4)	110.37(9)
O(4)-C(6)-H(6)	109.3
C(7)-C(6)-H(6)	109.3
C(4)-C(6)-H(6)	109.3
O(5)-C(7)-C(6)	109.69(9)
O(5)-C(7)-C(9)	103.51(9)
C(6)-C(7)-C(9)	108.53(10)
O(5)-C(7)-H(7)	111.6
C(6)-C(7)-H(7)	111.6
C(9)-C(7)-H(7)	111.6
O(7)-C(8)-O(6)	123.62(13)
O(7)-C(8)-O(5)	123.70(13)
O(6)-C(8)-O(5)	112.67(11)
O(6)-C(9)-C(10)	110.83(11)
O(6)-C(9)-C(7)	103.72(9)
C(10)-C(9)-C(7)	109.31(10)
O(6)-C(9)-H(9)	110.9
C(10)-C(9)-H(9)	110.9
C(7)-C(9)-H(9)	110.9
N(1)-C(10)-C(9)	108.74(11)
N(1)-C(10)-C(11)	110.30(11)
C(9)-C(10)-C(11)	109.07(10)
N(1)-C(10)-H(10)	109.6
C(9)-C(10)-H(10)	109.6
C(11)-C(10)-H(10)	109.6
O(1)-C(11)-C(10)	109.83(11)
O(1)-C(11)-C(4)	105.38(9)
C(10)-C(11)-C(4)	108.88(10)
O(1)-C(11)-H(11)	110.9
C(10)-C(11)-H(11)	110.9
C(4)-C(11)-H(11)	110.9

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for h11sel3.

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	22(1)	41(1)	38(1)	-3(1)	1(1)	-7(1)
O(1)	29(1)	37(1)	34(1)	8(1)	1(1)	11(1)
O(2)	21(1)	24(1)	25(1)	3(1)	-1(1)	0(1)
O(3)	56(1)	33(1)	37(1)	-1(1)	3(1)	19(1)
O(4)	28(1)	26(1)	37(1)	3(1)	5(1)	-4(1)
O(5)	27(1)	36(1)	22(1)	-5(1)	0(1)	6(1)
O(6)	36(1)	44(1)	31(1)	-7(1)	1(1)	18(1)
O(7)	40(1)	50(1)	28(1)	-6(1)	9(1)	4(1)
C(1)	29(1)	28(1)	24(1)	3(1)	-1(1)	5(1)
C(2)	47(1)	27(1)	39(1)	6(1)	6(1)	-2(1)
C(3)	51(1)	44(1)	23(1)	1(1)	0(1)	9(1)
C(4)	21(1)	21(1)	24(1)	-2(1)	-1(1)	-1(1)
C(5)	39(1)	24(1)	32(1)	-7(1)	0(1)	-2(1)
C(6)	20(1)	21(1)	24(1)	0(1)	1(1)	0(1)
C(7)	22(1)	25(1)	21(1)	-3(1)	0(1)	-2(1)
C(8)	28(1)	28(1)	31(1)	-4(1)	2(1)	1(1)
C(9)	31(1)	25(1)	26(1)	-1(1)	1(1)	7(1)
C(10)	18(1)	38(1)	30(1)	-2(1)	-3(1)	3(1)
C(11)	22(1)	33(1)	25(1)	-2(1)	-4(1)	0(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for h11sel3.

	x	y	z	U(eq)
H(1)	1290(40)	4803(13)	3110(14)	56(6)
H(3)	9190(50)	3774(16)	1823(17)	70(7)
H(2A)	7945	7687	2149	56
H(2B)	7399	7951	1080	56
H(2C)	9690	7401	1336	56
H(3A)	6074	5608	319	59
H(3B)	8637	5978	262	59
H(3C)	6595	6643	-68	59
H(5A)	4875	3925	2171	38
H(5B)	6190	4343	1277	38
H(6)	7431	4901	3654	26
H(7)	7451	6587	3677	27
H(9)	4239	7335	3237	33
H(10)	1007	6411	2800	35
H(11)	2838	5439	1656	32

Table 1. Crystal data and structure refinement for h10sel3.

Identification code	h10sel3
Empirical formula	C14 H13 Br Fe O7
Formula weight	429.00
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P 2_1 2_1 2_1
Unit cell dimensions	a = 8.6252(3) A alpha = 90 deg. b = 8.6773(3) A beta = 90 deg. c = 43.7286(16) A gamma = 90 deg.
Volume	3272.8(2) A^3
Z, Calculated density	8, 1.741 Mg/m^3
Absorption coefficient	3.394 mm^-1
F(000)	1712
Crystal size	0.45 x 0.30 x 0.15 mm
Theta range for data collection	3.31 to 27.56 deg.
Limiting indices	-11<=h<=11, -10<=k<=11, -56<=l<=56
Reflections collected / unique	25844 / 6937 [R(int) = 0.0663]
Completeness to theta = 27.56	95.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6300 and 0.3104
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6937 / 0 / 429
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0437, wR2 = 0.0788
R indices (all data)	R1 = 0.0677, wR2 = 0.0860
Absolute structure parameter	0.011(9)
Largest diff. peak and hole	0.554 and -0.567 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for h10sel3.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Fe(1)	10630(1)	3004(1)	1789(1)	29(1)
C(10)	11952(6)	4506(7)	1691(1)	37(1)
O(10)	12725(4)	5543(5)	1637(1)	55(1)
C(20)	9414(5)	3129(5)	1460(1)	33(1)
O(20)	8621(4)	3203(5)	1252(1)	48(1)
C(30)	11935(7)	1555(7)	1656(1)	49(1)
O(30)	12798(6)	659(6)	1564(1)	82(2)
Br(1)	9092(1)	-631(1)	1945(1)	40(1)
O(1)	5849(4)	4037(4)	1661(1)	45(1)
O(2)	7164(4)	6167(4)	1767(1)	34(1)
O(3)	6991(3)	4460(4)	2354(1)	26(1)
O(4)	7042(3)	1862(4)	2372(1)	32(1)
C(1)	7613(5)	2229(5)	2075(1)	25(1)
C(2)	9181(5)	1552(5)	2031(1)	28(1)
C(3)	10416(5)	2056(5)	2218(1)	27(1)
C(4)	10515(5)	3662(5)	2237(1)	27(1)
C(5)	9388(5)	4487(6)	2071(1)	26(1)
C(6)	7726(5)	4003(5)	2075(1)	24(1)
C(7)	6801(5)	4696(5)	1809(1)	27(1)
C(8)	6394(5)	6928(6)	1514(1)	39(1)
C(9)	6190(5)	3148(5)	2481(1)	29(1)
C(11)	6334(6)	3219(7)	2823(1)	43(1)
C(12)	4525(5)	3111(6)	2376(1)	40(1)
Fe(2)	10537(1)	8236(1)	709(1)	31(1)
C(40)	12113(8)	9453(7)	814(1)	49(1)
C(50)	10325(5)	7159(6)	1058(1)	34(1)
C(60)	9096(8)	9641(7)	804(1)	52(2)
O(40)	13210(6)	10130(5)	881(1)	80(2)
O(50)	10073(5)	6542(4)	1279(1)	54(1)
O(60)	8167(6)	10514(6)	869(1)	86(2)
Br(2)	6891(1)	6719(1)	544(1)	39(1)
O(5)	11603(4)	3692(5)	904(1)	59(1)
O(6)	13814(4)	4496(4)	706(1)	36(1)
O(7)	11983(3)	4543(4)	163(1)	27(1)
O(8)	9357(4)	4498(4)	165(1)	34(1)
C(21)	9769(5)	5174(5)	451(1)	27(1)
C(22)	9099(5)	6770(5)	470(1)	29(1)
C(23)	9665(5)	7941(5)	278(1)	29(1)
C(24)	11290(6)	8018(5)	265(1)	32(1)
C(25)	12078(6)	6912(6)	448(1)	29(1)
C(26)	11539(5)	5273(5)	446(1)	24(1)
C(27)	12292(5)	4390(5)	715(1)	25(1)
C(28)	14656(6)	3757(6)	952(1)	37(1)
C(29)	10673(5)	3691(5)	53(1)	29(1)
C(31)	10679(7)	3765(6)	-290(1)	47(1)
C(32)	10713(6)	2062(5)	174(1)	44(1)

Table 3. Bond lengths [A] for h10sel3.

Fe(1)-C(30)	1.785(6)
Fe(1)-C(10)	1.785(6)
Fe(1)-C(20)	1.785(5)
Fe(1)-C(4)	2.044(4)
Fe(1)-C(3)	2.054(4)
Fe(1)-C(2)	2.066(5)
Fe(1)-C(5)	2.079(5)
C(10)-O(10)	1.143(6)
C(20)-O(20)	1.141(5)
C(30)-O(30)	1.149(6)
Br(1)-C(2)	1.933(4)
O(1)-C(7)	1.193(5)
O(2)-C(7)	1.326(5)
O(2)-C(8)	1.451(5)
O(3)-C(6)	1.432(5)
O(3)-C(9)	1.444(5)
O(4)-C(9)	1.420(5)
O(4)-C(1)	1.423(5)
C(1)-C(2)	1.487(6)
C(1)-C(6)	1.543(6)
C(2)-C(3)	1.410(6)
C(3)-C(4)	1.399(6)
C(4)-C(5)	1.410(6)
C(5)-C(6)	1.494(6)
C(5)-H(5)	0.85(4)
C(6)-C(7)	1.532(6)
C(9)-C(11)	1.500(6)
C(9)-C(12)	1.509(6)
Fe(2)-C(40)	1.782(7)
Fe(2)-C(60)	1.790(6)
Fe(2)-C(50)	1.799(5)
Fe(2)-C(23)	2.042(4)
Fe(2)-C(24)	2.057(5)
Fe(2)-C(22)	2.061(4)
Fe(2)-C(25)	2.096(5)
C(40)-O(40)	1.151(7)
C(50)-O(50)	1.125(5)
C(60)-O(60)	1.139(7)
Br(2)-C(22)	1.933(4)
O(5)-C(27)	1.184(5)
O(6)-C(27)	1.317(5)
O(6)-C(28)	1.447(5)
O(7)-C(29)	1.433(5)
O(7)-C(26)	1.441(5)
O(8)-C(29)	1.421(5)
O(8)-C(21)	1.426(5)
C(21)-C(22)	1.503(6)
C(21)-C(26)	1.528(6)
C(22)-C(23)	1.404(6)
C(23)-C(24)	1.405(7)
C(24)-C(25)	1.422(7)
C(25)-C(26)	1.496(7)
C(25)-H(25)	0.93(4)
C(26)-C(27)	1.547(6)
C(29)-C(31)	1.500(6)
C(29)-C(32)	1.509(6)

Table 4. Bond lengths [A] and angles [deg] for h10sel3.

C(30)-Fe(1)-C(10)	91.9(2)
C(30)-Fe(1)-C(20)	98.7(2)
C(10)-Fe(1)-C(20)	97.8(2)
C(30)-Fe(1)-C(4)	122.7(2)
C(10)-Fe(1)-C(4)	93.3(2)
C(20)-Fe(1)-C(4)	136.7(2)
C(30)-Fe(1)-C(3)	94.1(2)
C(10)-Fe(1)-C(3)	124.7(2)
C(20)-Fe(1)-C(3)	135.03(19)
C(4)-Fe(1)-C(3)	39.93(17)
C(30)-Fe(1)-C(2)	96.8(2)
C(10)-Fe(1)-C(2)	162.8(2)
C(20)-Fe(1)-C(2)	95.5(2)
C(4)-Fe(1)-C(2)	69.49(17)
C(3)-Fe(1)-C(2)	40.01(17)
C(30)-Fe(1)-C(5)	162.6(2)
C(10)-Fe(1)-C(5)	91.1(2)
C(20)-Fe(1)-C(5)	97.92(19)
C(4)-Fe(1)-C(5)	39.97(17)
C(3)-Fe(1)-C(5)	70.20(18)
C(2)-Fe(1)-C(5)	76.24(18)
O(10)-C(10)-Fe(1)	175.0(5)
O(20)-C(20)-Fe(1)	179.1(4)
O(30)-C(30)-Fe(1)	177.6(5)
C(7)-O(2)-C(8)	115.8(4)
C(6)-O(3)-C(9)	108.9(3)
C(9)-O(4)-C(1)	108.1(3)
O(4)-C(1)-C(2)	110.1(3)
O(4)-C(1)-C(6)	104.3(4)
C(2)-C(1)-C(6)	109.7(4)
C(3)-C(2)-C(1)	119.4(4)
C(3)-C(2)-Br(1)	116.6(3)
C(1)-C(2)-Br(1)	112.1(3)
C(3)-C(2)-Fe(1)	69.5(3)
C(1)-C(2)-Fe(1)	112.0(3)
Br(1)-C(2)-Fe(1)	121.4(2)
C(4)-C(3)-C(2)	113.0(4)
C(4)-C(3)-Fe(1)	69.6(3)
C(2)-C(3)-Fe(1)	70.4(3)
C(3)-C(4)-C(5)	115.6(4)
C(3)-C(4)-Fe(1)	70.4(3)
C(5)-C(4)-Fe(1)	71.4(3)
C(4)-C(5)-C(6)	120.9(4)
C(4)-C(5)-Fe(1)	68.7(3)
C(6)-C(5)-Fe(1)	109.1(3)
O(3)-C(6)-C(5)	110.9(3)
O(3)-C(6)-C(7)	107.9(3)
C(5)-C(6)-C(7)	112.4(4)
O(3)-C(6)-C(1)	104.3(4)
C(5)-C(6)-C(1)	109.9(4)
C(7)-C(6)-C(1)	111.1(4)
O(1)-C(7)-O(2)	123.3(4)
O(1)-C(7)-C(6)	125.6(4)
O(2)-C(7)-C(6)	111.1(4)
O(4)-C(9)-O(3)	104.0(3)
O(4)-C(9)-C(11)	109.0(4)

O(3)-C(9)-C(11)	108.3(4)
O(4)-C(9)-C(12)	111.9(4)
O(3)-C(9)-C(12)	110.7(4)
C(11)-C(9)-C(12)	112.6(4)
C(40)-Fe(2)-C(60)	93.8(3)
C(40)-Fe(2)-C(50)	99.6(2)
C(60)-Fe(2)-C(50)	95.0(2)
C(40)-Fe(2)-C(23)	126.4(2)
C(60)-Fe(2)-C(23)	92.5(2)
C(50)-Fe(2)-C(23)	132.8(2)
C(40)-Fe(2)-C(24)	93.3(2)
C(60)-Fe(2)-C(24)	120.1(2)
C(50)-Fe(2)-C(24)	141.8(2)
C(23)-Fe(2)-C(24)	40.08(18)
C(40)-Fe(2)-C(22)	162.9(2)
C(60)-Fe(2)-C(22)	96.9(2)
C(50)-Fe(2)-C(22)	92.8(2)
C(23)-Fe(2)-C(22)	40.00(18)
C(24)-Fe(2)-C(22)	69.78(18)
C(40)-Fe(2)-C(25)	88.9(2)
C(60)-Fe(2)-C(25)	160.1(2)
C(50)-Fe(2)-C(25)	104.0(2)
C(23)-Fe(2)-C(25)	70.30(18)
C(24)-Fe(2)-C(25)	40.04(18)
C(22)-Fe(2)-C(25)	76.53(17)
O(40)-C(40)-Fe(2)	174.2(6)
O(50)-C(50)-Fe(2)	174.2(4)
O(60)-C(60)-Fe(2)	178.4(6)
C(27)-O(6)-C(28)	116.6(4)
C(29)-O(7)-C(26)	107.8(3)
C(29)-O(8)-C(21)	107.8(3)
O(8)-C(21)-C(22)	109.3(4)
O(8)-C(21)-C(26)	105.1(4)
C(22)-C(21)-C(26)	109.5(4)
C(23)-C(22)-C(21)	120.1(4)
C(23)-C(22)-Br(2)	117.4(3)
C(21)-C(22)-Br(2)	111.5(3)
C(23)-C(22)-Fe(2)	69.3(3)
C(21)-C(22)-Fe(2)	111.4(3)
Br(2)-C(22)-Fe(2)	121.4(2)
C(22)-C(23)-C(24)	114.0(4)
C(22)-C(23)-Fe(2)	70.7(3)
C(24)-C(23)-Fe(2)	70.5(3)
C(23)-C(24)-C(25)	114.9(4)
C(23)-C(24)-Fe(2)	69.4(3)
C(25)-C(24)-Fe(2)	71.5(3)
C(24)-C(25)-C(26)	119.3(4)
C(24)-C(25)-Fe(2)	68.5(3)
C(26)-C(25)-Fe(2)	109.0(3)
O(7)-C(26)-C(25)	109.8(3)
O(7)-C(26)-C(21)	104.7(4)
C(25)-C(26)-C(21)	111.4(4)
O(7)-C(26)-C(27)	108.9(3)
C(25)-C(26)-C(27)	109.6(4)
C(21)-C(26)-C(27)	112.3(4)
O(5)-C(27)-O(6)	123.8(4)
O(5)-C(27)-C(26)	125.0(4)
O(6)-C(27)-C(26)	111.2(4)
O(8)-C(29)-O(7)	105.1(3)
O(8)-C(29)-C(31)	109.0(4)
O(7)-C(29)-C(31)	108.1(4)

O(8)-C(29)-C(32)	111.0(4)
O(7)-C(29)-C(32)	110.4(4)
C(31)-C(29)-C(32)	112.9(4)

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for h10sel3. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Fe(1)	30(1)	36(1)	20(1)	-1(1)	1(1)	3(1)
C(10)	29(3)	52(3)	32(3)	-6(3)	-4(2)	2(3)
O(10)	37(2)	68(3)	59(3)	3(2)	3(2)	-20(2)
C(20)	37(3)	30(3)	32(3)	-5(2)	11(2)	-6(3)
O(20)	48(2)	76(3)	19(2)	0(2)	-8(2)	-13(2)
C(30)	58(3)	61(4)	27(3)	6(3)	15(3)	19(3)
O(30)	109(4)	78(3)	58(3)	13(3)	42(3)	52(3)
Br(1)	59(1)	28(1)	34(1)	-3(1)	-5(1)	7(1)
O(1)	46(2)	37(2)	53(2)	3(2)	-30(2)	-7(2)
O(2)	37(2)	30(2)	33(2)	9(1)	-10(2)	-9(2)
O(3)	24(2)	28(2)	25(2)	0(1)	3(1)	-1(2)
O(4)	31(2)	28(2)	35(2)	6(2)	7(2)	2(2)
C(1)	24(2)	26(3)	23(2)	2(2)	-2(2)	-2(2)
C(2)	40(3)	26(2)	18(2)	-1(2)	-2(2)	0(2)
C(3)	30(2)	37(3)	15(2)	2(2)	3(2)	7(2)
C(4)	26(2)	38(3)	18(2)	-5(2)	-3(2)	-2(2)
C(5)	24(2)	29(3)	24(2)	-4(2)	1(2)	-8(2)
C(6)	22(2)	31(3)	19(2)	1(2)	-3(2)	1(2)
C(7)	28(2)	29(3)	24(2)	0(2)	-1(2)	-1(2)
C(8)	42(3)	34(3)	40(3)	13(2)	-11(2)	-6(2)
C(9)	26(2)	28(3)	33(2)	1(2)	5(2)	-1(2)
C(11)	39(3)	56(3)	34(3)	6(3)	9(2)	2(3)
C(12)	28(3)	40(3)	53(3)	4(3)	2(2)	-6(3)
Fe(2)	48(1)	24(1)	21(1)	0(1)	-1(1)	1(1)
C(40)	82(4)	32(3)	32(3)	2(3)	8(3)	-9(4)
C(50)	40(3)	35(3)	27(3)	1(2)	1(2)	3(2)
C(60)	79(4)	46(4)	33(3)	-8(3)	-19(3)	11(4)
O(40)	101(4)	79(4)	58(3)	-20(2)	6(3)	-54(3)
O(50)	72(3)	53(3)	36(2)	16(2)	7(2)	-2(2)
O(60)	108(4)	73(3)	76(4)	-33(3)	-25(3)	54(3)
Br(2)	34(1)	50(1)	33(1)	4(1)	2(1)	11(1)
O(5)	34(2)	84(3)	59(3)	46(2)	7(2)	4(2)
O(6)	34(2)	39(2)	33(2)	9(2)	-10(2)	-1(2)
O(7)	29(2)	30(2)	22(2)	-1(1)	3(1)	-3(2)
O(8)	33(2)	29(2)	39(2)	-10(2)	-7(2)	0(2)
C(21)	33(3)	20(2)	29(3)	1(2)	2(2)	2(2)
C(22)	32(2)	32(2)	22(2)	-2(2)	-1(2)	3(2)
C(23)	37(3)	30(3)	21(2)	-1(2)	-1(2)	9(2)
C(24)	52(3)	20(2)	23(2)	2(2)	5(2)	-4(2)
C(25)	28(2)	25(3)	32(2)	2(2)	3(2)	-3(2)
C(26)	27(3)	23(3)	23(2)	0(2)	3(2)	0(2)
C(27)	28(3)	26(2)	22(2)	1(2)	-2(2)	2(2)
C(28)	39(3)	37(3)	34(3)	2(2)	-19(2)	0(2)
C(29)	30(2)	26(2)	30(3)	-3(2)	-2(2)	-2(2)
C(31)	57(3)	51(3)	34(3)	-6(2)	-11(3)	-11(3)
C(32)	44(3)	21(2)	67(4)	-3(2)	5(3)	0(2)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for h10sel3.

	x	y	z	U(eq)
H(1)	6883	1862	1913	30
H(3)	11108	1375	2319	33
H(4)	11291	4164	2355	33
H(8A)	6639	6388	1323	58
H(8B)	6753	7998	1500	58
H(8C)	5271	6914	1547	58
H(11A)	5835	2313	2913	65
H(11B)	5829	4155	2899	65
H(11C)	7433	3234	2880	65
H(12A)	4493	2989	2153	61
H(12B)	4012	4078	2433	61
H(12C)	3988	2244	2473	61
H(21)	9404	4523	625	33
H(23)	9008	8622	168	35
H(24)	11823	8752	142	38
H(28A)	14395	4257	1147	55
H(28B)	15772	3849	915	55
H(28C)	14370	2665	962	55
H(31A)	9735	3281	-369	71
H(31B)	11589	3218	-369	71
H(31C)	10717	4844	-355	71
H(32A)	10663	2080	397	66
H(32B)	11676	1561	109	66
H(32C)	9824	1487	93	66
H(25)	13140(50)	7050(50)	436(9)	17(10)
H(5)	9480(40)	5460(50)	2082(9)	13(11)